AUS DER KLINIK FÜR ALLGEMEIN-, VISZERAL-, GEFÄß- UND

TRANSPLANTATIONSCHIRURGIE

DER LUDWIG-MAXIMILIANS-UNIVERSITÄT ZU MÜNCHEN

DIREKTOR: PROF. DR. MED. J. WERNER

PRÄDIKTIVE UND PROGNOSTISCHE FAKTOREN NACH RESEKTION GASTROINTESTINALER TUMORE

HABILITATIONSSCHRIFT

FÜR DAS FACH CHIRURGIE

DER MEDIZINISCHEN FAKULTÄT

VORGELEGT VON DR. MED. TOBIAS SIMON SCHIERGENS

2017

Inhaltsverzeichnis

1. Einleitung

Maligne Tumore des Gastrointestinaltrakts und ihre Metastasen stellen einen wesentlichen Anteil der Krebsneuerkrankungen sowie der Krebs-bedingten Todesursachen in Deutschland dar (Robert Koch Institut, 2015). Der operativen Entfernung dieser Tumore mit dem Aspekt eines kurativen Therapieziels kommt entscheidende Bedeutung zu, stellt sie für den Patienten bei den allermeisten dieser Malignome die die einzige Möglichkeit dar, von seinem Tumorleiden geheilt zu werden. Die Identifizierung bezüglich Morbidität, Rekurrenz und Gesamtüberleben relevanter Patienten- und Tumorcharakteristika, also von Risikofaktoren und Markern, ist von entscheidender Bedeutung. Sie ermöglicht es, die Prognose des Patienten besser abschätzen zu können, Subgruppen mit schlechterem oder besserem Überleben und somit Risikokonstellationen zu identifizieren und damit die Patientenselektion für die chirurgische Therapie zu verbessern. Ein spezieller Aspekt besteht in der Identifizierung von präoperativ beeinflussbaren Risikofaktoren, die auf die Möglichkeit der Optimierung des perioperativen Managements hinweisen. Ein weiterer Ansatzpunkt liegt in der Verbesserung der Entscheidungsgrundlagen für die adjuvante Therapie nach Resektion, was insbesondere durch Subklassifizierung einer Patientengruppe und Spezifizierung der Prognose von Patienten aus Kohorten von entscheidender Bedeutung ist, welche große inter-individuelle Unterschiede in Rekurrenz und Überleben aufweisen. Dieser Ansatz bietet die Möglichkeit, das Überleben von Patienten mit schlechterer Prognose durch eine im idealen Falle wirksame Therapie zu verbessern und zudem solche Patienten mit ohnehin guter Prognose zu identifizieren, bei denen die adjuvante Therapie nicht nur unwirksam ist, sondern im Rahmen derer die unerwünschten Wirkungen im Vordergrund stehen. Neben der Reduzierung der so verursachten Morbidität ist die Senkung der Therapiekosten zuletzt ebenfalls von Interesse.
Die Identifizierung und klinische Etablierung derartiger Variablen und Marker hat in den letzten Jahren in der Therapie zahlreicher gastrointestinaler Tumore erhebliche Fortschritte mit sich gebracht und die Prognose zahlreicher Tumorerkrankungen in der Viszeralmedizin

verbessert. Allerdings blieben zahlreiche Aspekte der Patientenselektion und relevanter Risikofaktoren beispielsweise bei der Resektion kolorektaler Lebermetastasen offen.

Im Rahmen der vorliegenden Arbeiten wurden prädiktiv und prognostisch relevante Faktoren im Rahmen der Leberresektion unter besonderer Berücksichtigung kolorektaler Lebermetastasen identifiziert und deren Relevanz diskutiert. Aufgrund der in der letzten Dekade zunehmenden Bedeutung der hepatischen Metastasektomie beim kolorektalen Karzinom lassen sich anhand der nun zu erhebenden Langzeit-Überlebensdaten dieser Patienten zuvor nicht identifizierbare Risikofaktoren beschreiben und erörtern (Quan et al. 2012; Schiergens et al. 2015b). Dies kann die Patientenselektion und das perioperative Management verbessern. Ferner wurden prädiktiv und prognostisch relevante Aspekte des Papillenkarzinoms anhand einer klinisch und molekularpathologisch untersuchten Kohorte identifiziert und deren Bedeutung im wissenschaftlichen Kontext der aktuellen Evidenz zur Diagnostik, Therapie und Prognose diskutiert.

2. Teilprojekte und Bedeutung der Arbeiten für das Fachgebiet

2.1 Identifizierung prädiktiver und prognostischer Faktoren nach Leberresektionen unter besonderer Berücksichtigung kolorektaler Lebermetastasen

Die Leber ist das am häufigsten von Fernmetastasen des kolorektalen Karzinoms (CRC) betroffene Organ. Etwa die Hälfte der Patienten mit CRC entwickelt im Laufe der Erkrankung Lebermetastasen (Cooper et al. 1995; Jemal et al. 2011). Die Resektion kolorektaler Lebermetastasen (CRLM) eingebettet in eine multimodale, interdisziplinäre Therapiestrategie ist heute etablierter Behandlungsstandard auf dem Boden guter Evidenz hinsichtlich Überleben und Verbesserung der Lebensqualität (Brown et al. 2010; Quan et al. 2012). Sie hat Einzug in die S3-Leitlinie gehalten (Pox et al. 2013), in der die operative Entfernung resektabler Lebermetastasen (Poston et al. 2005) empfohlen wird. Der chirurgischen Behandlung kolorektaler Lebermetastasen ist damit in den letzten Jahren eine zunehmende Bedeutung zugekommen. Dabei werden die operativen Resektionsstrategien auf dieser Evidenzgrundlage zunehmend aggressiver und die Indikationen großzügiger gestellt. Die Rechtfertigung der kontinuierlichen Ausweitung der Operationsindikation beispielsweise auch auf bilobär auftretende Lebermetastasen mit auch mehrzeitigen hepatischen Resektionsstrategien (Schadde et al. 2015; Schnitzbauer et al. 2012) basiert auf angesichts des metastasierten Tumorleidens exzellenten Überlebensraten bei diesen Patienten (Fong et al. 1997; Kim et al. 2011; Nordlinger et al. 1996; Scheele et al. 2001; Schiergens et al. 2015b). Die Heterogenität der Patientenpopulation mit CRLM, welcher interindividuelle Unterschiede in Zeitpunkt, Ausmaß und Dynamik der hepatischen Manifestation sowie auch in extrahepatischer Manifestation der Tumorerkrankung zu Grunde liegen, bedeutet in der interdisziplinären Entscheidung bezüglich Patientenselektion, Resektionsstrategie und multimodaler Therapie eine große Herausforderung für die individuelle Therapieplanung. Dies macht die Identifizierung prädiktiv (Morbidität) als auch prognostisch (Mortalität, Rekurrenz-freies Überleben, Gesamtüberleben) relevanter Faktoren in dieser Population erforderlich, um durch eine

sorgfältige Patientenselektion sowie das Anpassen des perioperativen Managements Morbidität, Mortalität und Langzeitüberleben dieser Patienten weiter zu verbessern. Diesbezüglich ist der *Fong-Score* ein in der Literatur etablierter und international anerkannter Prognoseindex, in dem insbesondere onkologische Risikovariablen wie Metastasengröße und -anzahl erfasst sind (Fong et al. 1999). Die allgemeine Gültigkeit und die Beschränkung auf die in diesem *Score* erfassten Risikovariablen ist jedoch in den letzten Jahren zunehmend in kritische Diskussion geraten. Im Fokus dieses Teils des Habilitationsprojekts stand daher neben etablierten und in derartigen Prognose-Indices eingegangenen onkologischen Variablen die Identifizierung weiterer prädiktiv und prognostisch relevanter Variablen unter besonderer Berücksichtigung der Evaluation von Patientenalter, Komorbiditäten sowie intraoperativem Blutverlust und perioperativer allogener Erythrozytentransfusion. Grundlage der retrospektiven Analyse dieser prädiktiven und prognostischen Faktoren in den vorliegenden Arbeiten sind die Daten von zwischen 2003 und 2013 einer elektiven Leberresektion zugeführten Patienten.

2.1.1 Morbidität und Mortalität nach Leberresektionen: Ermittlung der akuten postoperativen Phase

Leberresektionen zählen unter den viszeralchirurgischen Ein-Höhlen-Eingriffen zu den Operationen mit der höchsten Morbidität und Mortalität (Belghiti et al. 2000; Dimick et al. 2003; Jarnagin et al. 2002; Virani et al. 2007). Jedoch gelang es in den vergangenen Dekaden, Morbidität und Mortalität durch Verbesserungen des perioperativen bzw. intensivmedizinischen Managements sowie der operativen Technik der Leberresektion deutlich zu senken (Jarnagin et al. 2002; Virani et al. 2007). Je nach Charakteristik der jeweiligen Patientenpopulationen liegt die Mortalitätsrate in Zentren inzwischen durchschnittlich um 6% (Schiergens et al. 2015a). Neben onkologischen Faktoren stellt die Berücksichtigung der perioperativen Morbidität und Mortalität wie beschrieben einen entscheidenden Faktor für eine erfolgreiche Patientenselektion in der Leberchirurgie dar. Für den Vergleich von operativen Techniken im Rahmen von Studien und zur

Identifizierung von relevanten Faktoren für das perioperative Risiko ist der Parameter der Mortalität im Sinne einer signifikanten klinischen Kennzahl dabei essentiell. Analysen hierzu stellen den Schlüssel zur Senkung der postoperativen Mortalität dar (Simons et al. 2009a). Auch für die Information und Aufklärung des Patienten und seiner Angehörigen (*informed consent*) spielt die qualitative Beschreibung aber auch die Bezifferung dieses Risikos eine entscheidende Rolle. Ein grundlegendes Problem bei der Definition und Analyse perioperativer Mortalität besteht in der nicht näher definierten und nicht standardisiert verwendeten Dauer der *akuten postoperativen Phase* (APP) nach Leberresektionen. So werden für diese periprozedurale, akute Sterbephase in den wissenschaftlichen Publikationen hierzu uneinheitlich 30-Tages- (Erdogan et al. 2009; Menon et al. 2006; Mullen et al. 2007; Nygard et al. 2012; Turrentine et al. 2006; Virani et al. 2007) oder 90-Tages- (Chang et al. 2014; Hyder et al. 2013; Melloul et al. 2012; Motoyama et al. 2015; Mullen et al. 2007; Reddy et al. 2011), alternativ auch die Krankenhausmortalität (*in-house-mortality*) (Asiyanbola et al. 2008; Dimick et al. 2003; Hamel et al. 2005; Simons et al. 2009a; Simons et al. 2009b) berichtet und analysiert.

Diese Heterogenität macht nicht nur den sinnvollen Vergleich der Sterberaten zwischen Studien oder Zentren etwa zur Überwachung der Versorgungsqualität unmöglich, sondern führt vielmehr zu Verzerrung und *Bias* in der Analyse und Interpretation der der Mortalität zu Grunde liegenden und zu analysierenden Risikofaktoren (Schiergens et al. 2015a). Deskriptiv waren in Vorarbeiten Beobachtungen publiziert, bei denen sich die 90-Tages-Mortalität nach größeren viszeralchirurgischen Eingriffen und Leberresektionen deutlich höher als die 30-Tages-Mortalität zeigte (Mullen et al. 2007; Swanson et al. 2014). Ziel der vorliegenden Arbeiten war es, mittels einer neuartigen statistischen Methode zur Schwellenwertbestimmung an *Hazard*-Kurven die APP statistisch zu ermitteln, damit zu objektivieren und hierzu eine Regressionsanalyse der statistisch korrekten Mortalitätsphase zur Identifizierung von relevanten Risikoparametern durchzuführen. Bei dieser neu entwickelten statistischen Methode ermittelt eine Serie von statistischen Tests zur Konstanz der postoperativen, tagesbasierten *Hazard*-Rate (die Wahrscheinlichkeit ab Tag $t + 1$ zu

versterben) in Abhängigkeit der Zeit (Zeitfunktion) den statistischen Umschlagspunkt und damit das Ende der APP (Schiergens et al. 2015a).

Die statistisch auf Boden der postoperativen, tagesbasierten *Hazard*-Kurve kalkulierte APP lag bei der untersuchten Patientenpopulation bei 80 Tagen mit einem 95%-Konfidenzintervall von 40 bis 100 Tagen (Schiergens et al. 2015a). Somit lag die statistisch ermittelte akute Sterbephase am nächsten zu der in der Literatur berichteten und analysierten 90-Tages-Mortalität, so dass geschlussfolgert werden konnte, dass diese der statistischen APP am nächsten und deren Heranziehen zu favorisieren ist. Die 80- und 90-Tages-Mortalität in unserem Kollektiv lag bei 7.0%. Ferner konnte gezeigt werden, dass das Berichten und Analysieren der 30-Tages-Mortalität (4.0%) oder der Krankenhaus-Mortalität (5.0%) zu einer Verzerrung durch Untererfassung (*underreporting bias*) führt. Insbesondere konnte beobachtet werden, dass vor allem septische Komplikationen, die am ehesten aufgrund der Verbesserungen in der intensivmedizinischen Therapie der Sepsis zu protrahierter Mortalität zu führen scheinen, weniger adäquat erfasst werden, wenn statt der 90-Tages die 30-Tages-Mortalität herangezogen wird (Schiergens et al. 2015a). Die später bzw. im Vergleich zu anderen Ursachen postoperativer Mortalität septisch bedingt verzögerte Mortalität kann damit diskutiert werden, dass septische Komplikationen in vielen individuellen Fällen zunächst erfolgreich intensivmedizinisch und interventionell therapiert werden können (mit im weiteren Verlauf sekundärem Therapieversagen), während Mortalität auf Boden akuter Blutungen, Pulmonalarterienembolien oder des akuten Koronarsyndroms oft fulminant und damit früher zu postoperativer Mortalität führen (Schiergens et al. 2015a). Es handelt sich um die bis dato erste Publikation, welche eine statistisch ermittelte und damit wissenschaftlich belastbare Aussage zur Länge des APP nach Leberresektionen machen konnte. Als unabhängige Risikofaktoren der 80-Tages-Mortalität in der multivariaten Regressionsanalyse wurden in unserer Studie das Vorliegen multipler oder schwerer Komorbiditäten (OR 2.19), eine eingeschränkte Leberfunktion (OR 2.54) und eine ausgedehnte Resektion an der Leber (OR 2.27) identifiziert (Schiergens et al. 2015a). In anderen Arbeiten waren u.a. ein fortgeschrittenes Patientenalter (Asiyanbola et

al. 2008; Chang et al. 2014; Jarnagin et al. 2002; Mullen et al. 2007; Reddy et al. 2011; Simons et al. 2009a; Simons et al. 2009b), männliches Geschlecht (Asiyanbola et al. 2008; Reddy et al. 2011; Virani et al. 2007), Komorbiditäten (Belghiti et al. 2000; Chang et al. 2014; Reddy et al. 2011; Simons et al. 2009a; Simons et al. 2009b; Virani et al. 2007), vorbestehende Lebererkrankungen (Asiyanbola et al. 2008; Chang et al. 2014; Jarnagin et al. 2002; Virani et al. 2007), das Ausmaß der Leberresektion (Asiyanbola et al. 2008; Belghiti et al. 2000; Chang et al. 2014; Jarnagin et al. 2002; Mullen et al. 2007; Simons et al. 2009a; Simons et al. 2009b), erhöhter Blutverlust (Jarnagin et al. 2002; Wei et al. 2003), die Notwendigkeit einer Bluttransfusion (Asiyanbola et al. 2008; Mullen et al. 2007; Wei et al. 2003) sowie die Versorgungsstufe der Einrichtung (Asiyanbola et al. 2008; Simons et al. 2009a; Simons et al. 2009b) beschrieben worden.

Auf Boden der Ergebnisse dieser Arbeit sollte nach Leberresektionen die 90-Tages-Mortalität, nicht die 30-Tages-Mortalität berichtet und analysiert werden. Letztere führt zur Untererfassung (*underreporting*) der „wahren" Mortalitätsrate und bei der Analyse von Risikofaktoren zu Verzerrungen. Insbesondere septische Komplikationen scheinen aufgrund der durch sie protrahiert bedingten Mortalität unterrepräsentiert.

2.1.2 Die Rolle des Patientenalters, der Komorbiditäten und des Blutverlusts bei Leberresektionen

Vor dem Hintergrund der epidemiologischen Entwicklung in den westlichen Ländern, welche durch eine mit steigender Lebenserwartung alternde Bevölkerung charakterisiert ist, nimmt auch die Anzahl der älteren und damit assoziiert komorbiden Patienten zu, bei denen ein viszeralchirurgisch-onkologischer Eingriff indiziert ist (Smith et al. 2009). Die Anzahl älterer Patienten, bei denen eine Leberresektion bei primären und sekundären Lebermalignomen durchgeführt wird, ist somit weltweit relevant gestiegen (Belghiti et al. 2000; Ijtsma et al. 2008; Petrowsky and Clavien 2005; Reddy et al. 2011). Angesichts der Alterung der sogenannten „*Baby-Boomer*-Generation" ist davon auszugehen, dass dadurch der Anteil der Krebs-bedingten Sterbefälle weiter zunehmen wird (Al-Refaie et al. 2010).

Ferner besteht die Hypothese, dass derartige Eingriffe in fortgeschrittenem Patientenalter trotz Verbesserungen und Fortschritte der Intensivmedizin sowie der chirurgischen Technik ein erhöhtes perioperatives Risiko auf Boden der Komorbidität sowie der reduzierten physiologischen Reserven dieser Patienten mit sich bringen. Der genauen Ausarbeitung der prognostischen Relevanz des Patientenalters, der Komorbiditäten sowie Alters-bezogener Risikofaktoren kommt somit eine entscheidende Rolle zu. In den hierzu durchgeführten Untersuchungen wurde daher in Bezug auf Morbidität und Gesamtüberleben die Rolle des Alters und der Komorbiditäten nach Leberresektionen untersucht. Bezüglich des Alters und der hier potentiell eingeschränkten physiologischen Reserven wurde ferner die Rolle des intraoperativen Blutverlusts analysiert.

Trotz eines bereits für eine Leberresektion selektierten Patientenguts zeigten sich ältere Patienten bezüglich der Art und Schwere der Komorbiditäten (erfasst durch die ASA-Klassifikation sowie den Charlson-Komorbiditäts-Index (CCI)) mit signifikant mehr sowie auch schwereren Komorbiditäten (Schiergens et al. 2014), ein zunächst per se trivialer und in der Literatur häufig beschriebener Zusammenhang (Al-Refaie et al. 2010; Aldrighetti et al. 2003; Hanazaki et al. 2001). Dies betraf insbesondere die Häufigkeit kardiovaskulärer Vorerkrankungen ($P < 0.001$) und des Diabetes mellitus ($P < 0.001$) (Schiergens et al. 2014). Ältere Patienten erlitten ferner signifikant häufiger schwere sowie nicht-chirurgische Komplikationen, wohingegen die Rate chirurgischer Komplikationen vergleichbar war.

Fortgeschrittenes Patientenalter erwies sich in der beschriebenen Studie sowohl univariat ($P < 0.001$) als auch in der multivariaten Analyse ($P < 0.001$) bezüglich des Gesamtüberlebens als signifikanter Risikofaktor (Schiergens et al. 2014). In der vorliegenden sowie auch in anderen chirurgischen Studien größerer Patientenkohorten mit längerer Nachbeobachtungsphase wurde das Patientenalter auch adjustiert an Komorbiditäten als signifikanter Risikofaktor für reduziertes Gesamtüberleben identifiziert (Menon et al. 2006). Dies ist auch damit zu begründen, dass unabhängig von operativem Eingriff sowie Erkrankung das Sterberisiko im Alter zunimmt (Schiergens et al. 2016a). Zusammenhänge zwischen Risikofaktoren und Überleben werden statistisch in der Regel

durch Cox-Regressionsmodelle ermittelt, die für jede Variable allerdings lediglich eine grobe Zusammenfassung des Effekts ermöglichen (Abadi et al. 2011). Insbesondere die Annahme einer zeitlichen Konstanz des Effekts des Patientenalters in Bezug auf das Gesamtüberleben ist angesichts längerer Nachbeobachtungsphasen nach derartigen Operationen fraglich, so dass bezweifelt werden muss, ob vor dem Hintergrund eines gesamtstatistischen Zusammenhangs in einem Cox-Modell fortgeschrittenes Patientenalter als Kontraindikation für einen onkologischen Eingriff an der Leber angesehen werden sollte. Die Notwendigkeit, diesen Aspekt eingehender zu untersuchen, wird durch Vorarbeiten unterstrichen, die andeuten, dass gerade ältere Patienten signifikant (auch im Vergleich zu jüngeren) von der chirurgischen Entfernung kolorektaler Lebermetastasen profitieren (Adam et al. 2010; Turrini et al. 2005; Zacharias et al. 2004). Die statistische Methode der Standard-Regressionsmodelle wie dem Cox-Modell ermöglicht lediglich eine Aussage zum Ausmaß, nicht aber zum zeitlichen Verlauf des Zusammenhangs einer Kovariable und dem Überleben. Gerade dieser wäre von großem Interesse. In einer weiteren Analyse wurde daher zur exakteren Bestimmung des Anteils und der Signifikanz des Patientenalters nach Leberresektionen unter besonderer Berücksichtigung der Resektion kolorektaler Lebermetastasen (*2.1.3.2*) eine multivariate Überlebens-Analyse mit einem sogenannten erweiterten Regressionsmodell, dem Cox-Aalen-Modell, durchgeführt. Dieses ermöglich die multivariate Beschreibung zeit-abhängiger Effekte einer Variable (Aalen 1989; Scheike and Zhang 2003). In der vorliegenden Arbeit zeigt sich in diesem Modell nach Ausschluss des Effekts der perioperativen Mortalität, dass adjustiert an prognostisch relevante *Confounder* Komorbiditäten und das Patientenalter in Bezug auf das Langzeitüberleben innerhalb der ersten 39 postoperativen Monate keinen signifikanten Einfluss hatten (Schiergens et al. 2016a). Aus einem altersstratifizierten Vergleich der prognostisch multivariat adjustierten Hazardkurven 70-jähriger Patienten mit Sterbetafeln des Statistischen Bundesamts konnte ferner beobachtet werden, dass das Sterberisiko eines älteren Patienten 66 Monate nach Operation relevant abfällt und bei 78 Monaten *post operationem* das Niveau der Allgemeinbevölkerung erreicht, was der „statistischen

Heilung" (*statistical cure*) des Patienten zu diesem Zeitpunkt entspricht (Schiergens et al. 2016a).

Aus den Ergebnissen dieser Arbeiten wurde geschlussfolgert, dass das Patientenalter per se keine Kontraindikation gegen eine Leberresektion darstellt. Vielmehr sind ältere Patienten einem höheren perioperativem Risiko ausgesetzt, nicht-chirurgische postoperative Komplikationen zu erleiden, die im Wesentlichen durch ihre insbesondere kardiovaskulären Komorbiditäten zu erklären sind. Diese sollten ergo im Besonderen bezüglich der Patientenselektion mit Blick auf das perioperative Risiko und damit auf nicht-chirurgische Morbidität und das Mortalitätsrisiko erfolgen. Allerdings sind somit auch nach sorgfältiger Patientenselektion ältere Patienten im Rahmen einer Leberresektion durch ihre Komorbiditäten gefährdet.

Durch abnehmende kardiopulmonale Reserven im Alter (Shirabe et al. 2009) könnten ältere Patienten ferner durch erhöhten intraoperativen Blutverlust gefährdet sein. Bei zwischen den Altersgruppen vergleichbarem intraoperativem Blutverlust in der oben beschriebenen Studie (Schiergens et al. 2014) waren in der Subgruppe der älteren Patienten signifikant häufiger und signifikant mehr Bluttransfusionen zu verzeichnen. Dies kann mit einer niedrigeren Transfusionsschwelle bei Patienten mit insbesondere kardiovaskulären Komorbiditäten erklärt werden (Al-Refaie et al. 2010; Schiergens et al. 2014). In der Alters-stratifizierten univariaten Analyse des Gesamtüberlebens in Abhängigkeit des intraoperativen Blutverlusts war zu beobachten, dass jüngere Patienten mit erhöhtem Blutverlust im Vergleich zu solchen mit niedrigem Blutverlust keinen signifikanten Unterschied im Gesamtüberleben aufwiesen ($P = 0.933$). Im Gegensatz hierzu zeigte diese Analyse bei Patienten älter als 70 Jahre einen signifikanten Überlebensunterschied ($P < 0.001$). In der multivariaten Regressionsanalyse der Gesamtkohorte wurden das Vorliegen von Komorbiditäten (CCI > 2) und ein erhöhter intraoperativer Blutverlust als signifikante unabhängige Risikofaktoren für das Auftreten postoperativer Komplikationen identifiziert (Schiergens et al. 2014). Diese Ergebnisse unterstreichen die Notwendigkeit der peniblen Reduzierung des intraoperativen Blutverlusts gerade bei älteren und komorbiden Patienten

(*2.1.3.3*) und eines optimalen perioperativen anästhesiologischen Management dieser Patienten. Als eine technische Strategie zur Reduzierung des Blutverlusts wurde der Einsatz des Pringle-Manövers zur Verringerung des hepatischen Blutzuflusses untersucht und diskutiert. Bei Patienten, bei denen dieses Manöver durchgeführt wurde, zeigte sich in dieser Studie keine erhöhte Morbidität (Schiergens et al. 2014).

2.1.3 Bedeutung der Metastasektomie kolorektaler Lebermetastasen

2.1.3.1 Überleben und prognostische Faktoren nach Resektion kolorektaler Lebermetastasen

Das in der vorliegenden Analyse erfasste mediane Gesamtüberleben des Kollektivs nach Resektion kolorektaler Lebermetastasen lag bei 58 Monaten (Schiergens et al. 2015b). Als unabhängige Risikofaktoren für das krankheitsfreie Überleben zeigte sich teils analog zu den gängigen, bereits in der Literatur beschriebenen *Scores* (Fong et al. 1999) die hepatische Tumorlast (Anzahl der Metastasen), die Resektion nicht im Gesunden (R1/R2) und die Durchführung einer perioperativen allogenen Bluttransfusion. Für das Gesamtüberleben wurden ein fortgeschrittenes Patientenalter (älter als 70 Jahre), Komorbiditäten, die Durchführung einer ausgedehnten Leberresektion und das Auftreten postoperativer Komplikationen identifiziert.

2.1.3.2 Bedeutung des Patientenalters und der Komorbidität

In der oben beschriebenen, das Cox-Aalen-Modell anwendenden Studie (Schiergens et al. 2016a) wurde eine Subgruppenanalyse der Patienten nach Resektion kolorektaler Lebermetastasen durchgeführt. Hier konnte beobachtet werden, dass der Effekt des Alters erst bei 70 Monaten nach Operation bezüglich des Gesamtüberlebens der Patienten relevant wurde und der Einfluss von Komorbiditäten 43 Monate nach Operation anstieg (Schiergens et al. 2016a). Mit Blick auf das angesichts eines metastasierten Tumorstadiums exzellente Gesamtüberleben nach Resektion kolorektaler Lebermetastasen betonen die

Ergebnisse dieser Arbeit, dass Patientenalter und Komorbiditäten zwar angesichts des perioperativen Risikos individuell betrachtet werden und die in die Patientenselektion mit einfließen müssen, aber grundsätzlich keine Kontraindikation gegen die Resektion darstellen.

2.1.3.3 Die onkologisch-prognostische Signifikanz der perioperativen allogenen Bluttransfusion

Für die perioperative allogene Bluttransfusion (Erythrozytentransfusion) im Rahmen der Resektion von Primärtumoren des kolorektalen Karzinoms gilt es derzeit als akzeptiert, dass diese mit einer signifikant früheren Tumorrekurrenz assoziiert ist [11,12]. Allerdings muss vor diesem Hintergrund auf die Problematik des Zusammenhangs von Transfusion und schlechteren Langzeit-Ergebnissen nach onkologisch-chirurgischen Eingriffen in retrospektiven Studien hingewiesen werden, da die Erfordernis einer Transfusion mit möglichen Risikofaktoren als statistischen Störgrößen assoziiert sein kann (Cata et al. 2013; Schiergens et al. 2015b). Allerdings existieren zur Assoziation zwischen Transfusion und früherer Rekurrenz kolorektaler Primärtumore auch prospektive Studien (Acheson et al. 2012; Amato and Pescatori 2006). Vergleichbar zum Effekt postoperativer Komplikationen wird eine frühere Tumorrekurrenz nach Transfusion mit einer Transfusions-bedingten perioperativen Immunomodulation (TRIM) erklärt, die durch die Transfusion von Leukozyten und weiterer immunogener Bestandteile, welche in (v.a. nicht-bestrahlten) Erythrozytenkonzentraten nachzuweisen sind, verursacht wird (Blajchman 2002; Cata et al. 2013; Ghio et al. 2011). Die Rolle der Bluttransfusion bei Resektion kolorektaler Lebermetastasen ist noch ungeklärt, ist jedoch angesichts des Langzeitüberlebens dieser Patientenkohorte und der nicht unerheblichen Transfusionsrate bei Leberresektionen, welche zu den viszeralchirurgischen Eingriffen mit den höchsten Blutverlusten zählen, von besonderem und zunehmenden Interesse.

In der durchgeführten Studie war bei 36% der Patienten eine Transfusion erforderlich. Risikofaktoren hierfür waren eine präoperativ bestehende Anämie, weibliches Geschlecht,

erhöhter intraoperativer Blutverlust und das Auftreten schwerer postoperativer Komplikationen. Patienten, welche eine Transfusion erhielten, zeigte ein signifikant verkürztes Krankheits-freies Überleben (32 vs. 72 Monate; $P = 0.008$). Patienten die mehr als zwei Erythrozytenkonzentrate perioperativ erhielten, wiesen ein weiter verkürztes Krankheits-freies Überleben auf (27 Monate; $P = 0.020$). Von entscheidender Bedeutung war die statistische Adjustierung an den intraoperativen Blutverlust. Nach Adjustierung an diesen sowie an andere mit dem Krankheits-freien Überleben assoziierte Confounder konnte beobachtet werden, dass sich die perioperative Transfusion als ein unabhängiger Risikofaktor für verkürztes Krankheitsfreies Überleben erwies.

Unter Einbeziehung möglicher Störgrößen durch die retrospektive Natur der vorliegenden Analyse, welche kritisch diskutiert wurden (Schiergens et al. 2015b), ist aus diesen Ergebnissen zu schlussfolgern, dass die perioperative Transfusion bei Resektion kolorektaler Lebermetastasen auch aus onkologischen Gesichtspunkten vermieden werden sollte. Mögliche Ansatzpunkte stellen die möglichst konservative Therapie einer präoperativ bestehenden Anämie (Eisen, Vitamin B12, Erythropoietin, etc.), Strategien zur Minimierung des intraoperativen Blutverlusts (Moggia et al. 2016) sowie die Evaluation niedrigerer Transfusionsschwellen dar.

2.1.4 Bedeutung der Metastasektomie nicht-kolorektaler Lebermetastasen

2.1.4.1 Überleben nach Resektion nicht-kolorektaler Lebermetastasen

In einer weiteren Arbeit wurde die Kohorte der Patienten mit nicht-kolorektalen (nicht-neuroendokrinen) Lebermetastasen (NCRNNE) untersucht. In der Literatur zeigt sich für eine Reihe nicht-kolorektaler, nicht-neuroendokriner Primärtumoren, deren Lebermetastasen reseziert werden, eine zunehmende Evidenz für den Nutzen der hepatischen Metastasektomie. Hierbei können aus den einzelnen Entitäten aufgrund der Heterogenität dieses Patientenkollektivs und angesichts der Unterschiede zwischen den international berichteten Kohorten (Fitzgerald et al. 2014) lediglich einzelne Aspekte des

Nutzens der Metastasenresektion herausgearbeitet werden. Ziel der Arbeit war die Identifizierung von Risikofaktoren und Entitäten mit besserem bzw. schlechterem Überleben, was wiederum eine Grundlage für eine bessere Patientenselektion für dieses Patientengut darstellen und somit der Verbesserung des Überlebens nach NCRNNE-Metastasenresektion dienen kann.

Lebermetastasen urogenitaler Tumore (OS: 45 Monate; RFS: 21 Monate) insbesondere Metastasen des Nierenzellkarzinoms (s. 2.1.4.2), wurden als Subgruppe mit gutem Überleben identifiziert (Schiergens et al. 2016b). Schlechtes Überleben zeigte sich insbesondere für die Gruppe der nicht-kolorektalen gastrointestinalen Tumore (Pankreas, Magen, u.a.; OS: 8 Monate; RFS: 7 Monate). Dies deckt sich mit bisher veröffentlichten Ergebnissen (Fitzgerald et al. 2014). Allerdings wies diese Patientengruppe einige Patienten mit Langzeit-Überleben auf, so dass geschlussfolgert wurde, dass diese Entitäten per se zwar keine Kontraindikation gegen eine Metastasenresektion darstellen, die Patientenselektion allerdings streng zu handhaben ist (Schiergens et al. 2016b). Als unabhängige Risikofaktoren für verkürztes Gesamtüberleben bei NCRNNE-Patienten wurden eine extrahepatische Tumormanifestation (HR 1.56, $P < 0.046$), die Anzahl der Lebermetastasen (N > 3; HR 1.90, $P < 0.024$), die Resektion nicht im Gesunden (R1/2, HR 1.82, $P < 0.025$) und das Auftreten postoperativer Komplikationen identifiziert (HR 1.53, $P < 0.048$)(Schiergens et al. 2016b). Diese Ergebnisse sollten bei der Indikationsstellung und Operationsplanung berücksichtigt werden, um die Patientenselektion zu verbessern und die Überlebensraten dieser heterogenen Gruppe weiter zu verbessern.

2.1.4.2 Match-Analyse mit Vergleich zu kolorektalen Lebermetastasen

Im *Match*-Vergleich mit Patienten mit kolorektalen Lebermetastasen zeigte sich, dass die NCRNNE-Patienten ein signifikant schlechteres Überleben aufwiesen (Gesamtüberleben (OS): 35 vs. 54 Monate; $P = 0.008$; Rezidiv- bzw. Progressions-freies Überleben (RFS): 15 vs. 29 Monate; $P = 0.004$) (Schiergens et al. 2016b). In einer separat *gematchten* Vergleichsanalyse zeigten sich Patienten mit Nierenzellkarzinom bezüglich des

Gesamtüberlebens vergleichbar mit dem kolorektalen Karzinom (50 vs. 51 Monate; P = 0.901), so dass bei dieser Entität die auch aggressivere Metastasektomie im Bereich der Leber in Bezug auf einen onkologischen Nutzen gerechtfertigt zu sein scheint.

2.2 Das Papillenkarzinom und seine Subtypen

Das Papillenkarzinom (PapCa) ist ein äußerst seltenes Malignom und stellt 0,2% der gastrointestinalen und lediglich 6% der periampullären Tumore (Howe et al. 1998). Wie andere periampulläre Tumore stellt die kurative Resektion im Gesunden im Rahmen einer Pankreatikoduodenektomie (Operation nach Kausch-Whipple bzw. nach Traverso-Longmire), die sich nach der makroskopischen Lokalisation des Tumors richtet, die Therapie der Wahl dar, wann immer Resektabilität und Operabilität gegeben sind (Yeo et al. 1998). Die weitere Evidenzlage zur Behandlung dieses Tumors, etwa zur adjuvanten Systemtherapie, ist nicht zuletzt aufgrund seiner Seltenheit schwach (Kim et al. 2011; Neoptolemos et al. 2012). Dies ist unter anderem in den großen inter-individuellen Unterschieden im Gesamtüberleben der Patienten zu begründen. Diese erschweren ferner die Interpretation klinischer Studien und die individuelle klinische Entscheidung in Bezug auf die Indikation und Art einer adjuvanten Chemotherapie (Chang et al. 2013; O'Connell et al. 2008; Yeo et al. 1998).

Die anatomische Region, aus der dieser Tumor entsteht, stellt eine Grenzregion verschiedener Epithelien dar wie etwa die der Papilla Vateri, des Duodenums, des Gallengangs sowie des Pankreas (Westgaard et al. 2013). Aus dieser Tatsache leitet sich die Hypothese ab, dass dem gemeinsamen makroskopischen Ursprung des Tumors an der Papille unterschiedliche Epithelien als mikroskopischem Ursprung des Tumors zu Grunde liegen und dies aus tumorbiologischen Gesichtspunkten von prädiktiver und prognostischer Relevanz ist. Ferner könnte dieser Aspekt eine Erklärung für die großen inter-individuellen Unterschiede im Gesamtüberleben sein und die erschwerten Bedingungen erklären, das individuelle *Outcome* der Patienten vorherzusagen.

Die Hypothese der vorliegenden Untersuchungen vor diesem Hintergrund war, dass sich die zwei histopathologischen Haupttypen des Papillenkarzinoms, der intestinale (IT) und pankreatobiliäre (PT) Typ, welche bereits in den 1990er Jahren beschrieben worden waren (Fischer and Zhou 2003; Kimura et al. 1994), in Tumorbiologie, Tumorcharakteristika, Prognose sowie Chemosensitivität unterscheiden. Der intestinale Typ ist durch tubuläre und vernetzte atypische Drüsen mit Ausbildung teils kribriformer Sekundärstrukturen gekennzeichnet, welche durch mehrreihiges Zylinderepithel ausgekleidet sind (Fischer and Zhou 2003; Gassler and Knuchel 2012). Es zeigt sich ein Wachstumsmuster, das dem kolorektalen Adenokarzinom ähnlich ist (Gassler and Knuchel 2012). Tumore vom pankreatobiliären Typ haben einfache oder verzweigte Drüsen mit in der Regel einreihigem, kubischem bis niedrig zylindrischem Epithel (Fischer and Zhou 2003). In Analogie zum duktalen Adenokarzinom des Pankreas (PDAC) zeigt sich der pankreatobiliäre Subtyp in desmoplastischem Stroma. Auch bezüglich Keratinen und Apomucinen zeigen die zwei Subtypen unterschiedliche immunhistochemische Expressionsprofile (Chang et al. 2013; Fischer and Zhou 2003; Gassler and Knuchel 2012). Tumoren vom intestinalen Typ exprimieren häufig die Marker CK20, CDX2 und MUC2, ß-Catenin und Villin, während der pankreatobiliäre Typ vorwiegend Positivität für den Marker CK7 zeigt (Chang et al. 2013; Fischer and Zhou 2003; Gassler and Knuchel 2012).

Für die vorliegenden Untersuchungen zum Papillenkarzinom wurden die Daten und Tumorproben von zwischen 1991 und 2012 an unserer Klinik resezierten periampulären Karzinomen retrospektiv analysiert und die Karzinome, welche von der Papilla Vateri ausgingen (Ausschluss periampullärer bzw. in die Papilla Vateri einwachsender Tumore, Papillenkarzinome im engeren Sinne), selektiert und analysiert. Die identifizierten Papillenkarzinome wurden durch zwei unabhängige Pathologen auf Basis der H&E-Färbung in IT-PapCa und PT-PapCa stratifiziert und mittels *Tissue Microarray* im Anschluss auf das o.g. immunhistochemische Expressionsprofil ausgewertet.

2.2.1 Überleben unter Berücksichtigung der Subklassifikation in intestinalen und pankreatobiliären Typ

Eine inzwischen als historisch anzusehende Meinung zur Ursache des besseren Überlebens von Patienten mit Papillenkarzinom im Vergleich zu Patienten mit duktalem Adenokarzinom des Pankreas stellt die Hypothese dar, dass Papillenkarzinome aufgrund der makroskopischen Lokalisation an der Papilla Vateri zum früheren Auftreten durch das Tumorwachstum bedingter Symptome wie dem schmerzlosen Ikterus führen und daher in früheren Tumorstadien diagnostiziert und therapiert werden. Die Betrachtung der Daten der vorliegenden Gesamtkohorte der Papillenkarzinome und der in den Arbeiten durchgeführte Vergleich mit einer *gematchten* PDAC-Kohorte widersprach dieser Überlegung zunächst nicht (37 vs. 17 Monate medianes Überleben, $P < 0.001$) (Kimura et al. 1994). Stratifiziert nach den Subtypen des PapCa war allerdings festzustellen, dass sich das Überleben der Gesamtpopulation der Papillenkarzinome aus exzellentem medianen Überleben der Patienten mit intestinal differenzierten Tumoren (98 Monate) und dem hoch signifikant ($P < 0.001$) schlechteren Überleben solcher mit pankreatobiliär differenzierten Tumoren (25 Monate) zusammensetzt, was zur Überlegung Anlass gibt, dass es sich um biologisch unterschiedliche Tumore handelt. Unterschiede im Gesamtüberleben der Subtypen waren bereits in anderen Arbeiten gezeigt worden (Chang et al. 2013; Westgaard et al. 2013). In einer nun separat *gematchten* Analyse zeigte sich das Überleben der Patienten mit pankreatobiliär differenzierten Tumore vergleichbar (25 vs. 14 Monate, $P = 0.123$) mit dem der PDAC-Patienten (Schiergens et al. 2015c).

Trotz vergleichbarer Charakteristika in möglichen Störvariablen wie demographischen Parametern, präoperativer Symptomatik, Komorbiditäten und perioperativem Verlauf zeigten sich PT-Tumore im Vergleich zu IT-Tumoren in signifikant lokal weiter fortgeschrittenen Tumorstadien (pT3/4: 65% vs. 40%, $P = 0.022$; pN+ 67% vs. 28%, $P < 0.001$). Ferner waren in der PT-Subgruppe tendenziell mehr *High-Grade* Tumore festzustellen (57% vs. 38%, $P = 0.060$) (Schiergens et al. 2015c). Dies weist in Analogie zu anderen intestinal und pankreatobiliär differenzierten Adenokarzinomen des

Gastrointestinaltrakts wie dem kolorektalen Karzinom und dem PDAC ebenfalls auf eine aggressivere Tumorbiologie des pankreatobiliären im Vergleich zum intestinalen Subtyp hin (Gassler and Knuchel 2012). Im Rahmen einer multivariaten Regressionsanalyse bezüglich des Gesamtüberlebens wurden fortgeschrittenes Patientenalter (HR 1.70), das Auftreten postoperativer Komplikationen (HR 3.06), der pankreatobiliäre Subtyp (HR 2.50) und das Vorliegen von Lymphknotenmetastasen (pN+, HR 2.07) als unabhängige prognostische Risikofaktoren identifiziert. Somit stellt das Vorhandensein des pankreatobiliären im Vergleich zum intestinalen Tumortyp einen u.a. von der lymphogenen Metastasierung unabhängigen Risikofaktor für ein verkürztes Gesamtüberleben dar.

Bei der Entität des Papillenkarzinoms scheint es sich somit nicht um eine homogene Tumorentität zu handeln. Aus den Daten der vorliegenden Arbeiten lässt sich zum einen schlussfolgern, dass den Unterschieden im Überleben zwischen Papillenkarzinom und Pankreaskarzinom nicht die makroskopische Lokalisation zugrunde zu liegen scheint, sondern eine relevant unterschiedliche Tumorbiologie der beiden Subtypen des Papillenkarzinoms, die sich in signifikant fortgeschritteneren Tumorstadien bei Patienten mit pankreatobiliären Tumoren zeigt. Hierbei scheint der pankreatobiliäre Typ in Bezug auf lokale Tumoraggressivität und Überleben mit dem Pankreaskarzinom vergleichbar.

2.2.2 Wertigkeit der molekularen Phänotypisierung

Neben der histomorphologischen Charakterisierung wurde wie oben beschrieben in den vorliegenden Arbeiten auch die prädiktive und prognostische Wertigkeit einer Immunphänotypisierung des Papillenkarzinoms untersucht (Schiergens et al. 2015c). MUC2 (88%) und CK20 (83%) zeigten hierbei zunächst den besten positiv prädiktiven Wert in Bezug auf die histomorphologische Klassifizierung (H&E). CK7 zeigte diesbezüglich die höchste Sensitivität (81%). Unter Betrachtung des prognostischen Nutzens war die histomorphologische Klassifizierung in der univariaten Überlebens-Analyse am aussagekräftigsten (HR 2.38, $P < 0.001$). Die Marker CK7 (HR 1.86, $P = 0.028$) und MUC2 (HR 0.51, $P = 0.040$) erwiesen sich ebenfalls als prognostisch signifikant im Hinblick auf das

Gesamtüberleben. In einer anderen Arbeit wurden CDX2 und MUC1 als prognostisch signifikante Marker identifiziert (Chang et al. 2013). In dieser Studie war eine Subgruppe mit sehr schlechtem Überleben als solche mit pankreatobiliärem Phänotyp, CDX2-Negativität sowie MUC1-Positivität beschrieben worden, während eine Subgruppe mit gutem Überleben als eine solche mit intestinalem Subtyp und CDX2-Positivität berichtet worden war (Chang et al. 2013). Patienten aus unserer Kohorte mit Tumoren, welche eine pankreatobiliäre Differenzierung aufwiesen und deren Tumore CK7-Positivität (HR 3.37, $P < 0.001$) oder MUC2-Negativität (HR=2.73, $P = 0.004$) aufwiesen, zeigten sich im Vergleich zur alleinigen histomorphologischen Subtypisierung mit verschlechtertem Gesamtüberleben (Schiergens et al. 2015c). Die Prognose dieser Subgruppen konnte somit weiter spezifiziert werden. Darüber hinaus stellte der Kanon der aufgeführten Marker der Immunphänotypisierung eine Hilfestellung dar, den Anteil der gemischt-differenzierten (sog. *mixed-type*) Tumore (9.5% der Gesamtpopulation) in einer Consensus-Entscheidung weiter einordnen zu können. In einer Subgruppenanalyse zeigte sich, dass das Gesamtüberleben von Patienten mit gemischt-differenzierten Tumoren tendenziell von dem prädominant vorherrschenden Phänotyp abhängt. Diese Resultate erklären auch die weitere prognostische Spezifizierung der Prognose durch die zusätzliche molekulare Phänotypisierung.

Die alleinige morphologische Klassifikation durch eine erfahrene Pathologin bzw. einen erfahrenen Pathologen auf Basis der H&E Färbung scheint ausreichend zu sein, um die Einordnung in die beiden Subtypen mit signifikantem prognostischen Nutzen sicher durchführen zu können. Die Erhebung des oben aufgeführten Kanons an immunhistochemischen Markern, insbesondere CK7 und MUC2, kann hilfreich sein, Mischtypen weiter einzuordnen und die Prognose weiter zu spezifizieren.

2.2.3 Effektivität der adjuvanten Chemotherapie nach Stratifizierung in die Subtypen

Derzeit existieren keine Empfehlungen zur Berücksichtigung des Subtyps bei Indikation und Art der adjuvanten Chemotherapie nach kurativer Resektion des Papillenkarzinoms

(Chang et al. 2013; Kim et al. 2011; Neoptolemos et al. 2012). In der Literatur wurden ferner bis dato keine Überlebens- oder Rekurrenzraten nach adjuvanter Chemotherapie unter Berücksichtigung der Subklassifikation in die zwei Subtypen berichtet. Allerdings erscheint es vor dem Hintergrund der in 2.2.1 und 2.2.2 erläuterten Daten sinnvoll und vielversprechend, die Klassifikation der zwei Subtypen angesichts onkologisch relevanter Unterscheide auch bei der Entscheidung bezüglich einer adjuvanten Chemotherapie nach kurativer Resektion zu beachten. In Vorarbeiten wurde ferner spekuliert, dass sich die Unterschiede in Histomorphologie, immunhistochemischem Profil und Prognose, denen eine grundlegend unterschiedliche Tumorbiologie zu Grunde zu liegen scheint, auch in unterschiedlichen Chemosensitivitätsprofilen widerspiegeln könnten (Chang et al. 2013). Aufgrund der bereits oben beschriebenen Analogie zu kolorektalem Karzinom und PDAC könnten Patienten mit intestinal differenzierten Tumoren bei gegebener Indikation (beispielsweise pN+ in Analogie zu anderen intestinal differenzierten Adenokarzinomen des Gastrointestinaltrakts) von einer adjuvanten Chemotherapie mit 5-FU oder Platin-haltigen Chemotherapeutika profitieren, während bei Patienten mit pankreatobiliärem Subtyp eine adjuvante Chemotherapie analog zur Adjuvanz des PDAC effektiv sein könnte (Chang et al. 2013; Schiergens et al. 2015c). Prospektive, die Subklassifizierung in intestinalen und pankreatobiliären Subtyp beachtende klinische, randomisierte Studien existieren nicht, könnten diese Frage jedoch klären.

In unserer retrospektiven Analyse konnte beobachtet werden, dass Patienten mit pankreatobiliär differenzierten Tumoren im Gegensatz zu solchen mit intestinal differenzierten Tumoren von einer adjuvanten Gemcitabine-basierten Chemotherapie zu profitieren scheinen. Beim pankreatobiliären Typ zeigten Patienten nach adjuvanter Monochemotherapie mit Gemcitabine trotz lokal weiter fortgeschrittener Tumore (s. 2.2.1) ein besseres Überleben (32 vs. 13 Monate, $P = 0.013$). Beim intestinalen Typ wiesen Patienten nach Chemotherapie ein schlechteres Überleben auf (35 vs. 112 Monate, $P = 0.193$). In beiden Subgruppen war insbesondere bei lokal fortgeschrittenen Tumorstadien (pN+, pT3/4) eine adjuvante Therapie in Unkenntnis des Subtyps, dessen Klassifikation

nicht zur Standardevaluation des pathologischen Befunds gehört hatte, durchgeführt worden. Damit war auch bei mehr Patienten mit pankreatobiliär differenzierten Tumoren eine adjuvante Chemotherapie durchgeführt worden. Eine Erklärung der Ergebnisse könnte daher sein, dass bei Patienten mit intestinalen Tumoren die Chemotherapie aus tumorbiologischen Gründen nicht effektiv gewesen war und daher diese Patienten, bei denen aufgrund des fortgeschrittenen Tumorstadiums eine (in Unkenntnis des Subtyps mutmaßlich nicht effektive) Chemotherapie erwogen wurde, ein schlechteres medianes Überleben aufwiesen (35 Monate). Bei den pankreatobiliär differenzierten Tumoren hingegen könnte Gemcitabine analog zum Pankreaskarzinom das Überleben verbessert haben. Diese Unterschiede zwischen den Subtypen im Ansprechen auf eine adjuvante Chemotherapie könnten darüber hinaus auch die erschwerte Detektion signifikanter Unterschiede im Überleben in klinischen Studien, welche die Subtypisierung nicht berücksichtigen, erklären (Chang et al. 2013; Schiergens et al. 2015c), da derartige Studienergebnisse durch den Anteil des histopathologischen Subtyps an der Gesamtkohorte beeinflusst worden sein könnten. Damit mögen die vorliegenden Ergebnisse eine Erklärung darstellen, warum in retrospektiven und prospektiven Studien wie der ESPAC-3-Studie, in welchen eine histomorphologische Subtypisierung nicht berücksichtigt worden war, kein eindeutiger Vorteil für die adjuvante Chemotherapie gezeigt wurde (Bhatia et al. 2006; Klinkenbijl et al. 1999; Neoptolemos et al. 2012; Sikora et al. 2005; Smeenk et al. 2007). In einer Post-hoc-Analyse der ESPAC-3-Studie wurde allerdings multivariat adjustiert an prognostisch relevante Variablen ein Überlebensvorteil beobachtet, was die Hypothese unterstützt, dass Tumoren mit schlechter Prognose von einer Chemotherapie profitieren (Chang et al. 2013; Kim et al. 2011; Neoptolemos et al. 2012). Derartige Tumoren mit schlechter Prognose könnten vorwiegend solche mit pankreatobiliärer Differenzierung gewesen sein. Aufgrund des retrospektiven Aspekts der vorliegenden Studie wurden die Ergebnisse mit Zurückhaltung interpretiert und auf die Notwendigkeit der Durchführung randomisiert-kontrollierter Studien zur Effektivität einer adjuvanten Chemotherapie unter Berücksichtigung des Subtyps hingewiesen (Schiergens et

al. 2015c). Die Ergebnisse der vorliegenden Arbeiten weisen allerdings darauf hin, dass bei der adjuvanten Chemotherapie nach kurativer Resektion des Papillenkarzinoms die Klassifikation in intestinalen und pankreatobiliären Typ berücksichtigt werden sollte.

3. Zusammenfassung

Maligne Tumore des Gastrointestinaltrakts stellen einen wesentlichen Anteil Krebs-bedingter Todesursachen in Deutschland dar. Die Identifizierung bezüglich Morbidität, Rekurrenz und Gesamtüberleben relevanter Risikofaktoren ist daher von entscheidender Bedeutung. Die durchgeführten Untersuchungen fokussierten sich auf die Rolle des Patientenalters, der Komorbiditäten, des intraoperativen Blutverlusts sowie der perioperativen Bluttransfusion nach Leberresektionen unter besonderer Berücksichtigung kolorektaler Lebermetastasen sowie auf die klinische Relevanz der histomorphologischen und molekularen Phänotypisierung des Papillenkarzinoms in seine Subtypen.

Ziel einer der Analysen war die exakte zeitliche Definition der Mortalitätsphase nach Leberresektionen. Die Problematik bestand in der in der Literatur heterogenen Publikation und Analyse nicht objektivierter, sich relevant voneinander unterscheidender Mortalitätsperioden. Mittels einer neuen statistischen Methode konnte die Dauer der Mortalitätsphase mit 80 Tagen erstmals objektiviert werden. Es wurde ferner gezeigt, dass die 30-Tages-Mortalität zu einer Untererfassung von insbesondere durch septische Komplikationen verursachter Mortalität führt. In weiteren Arbeiten wurde beobachtet, dass ältere Patienten bei Leberresektionen insbesondere aufgrund ihrer kardiovaskulären Komorbiditäten einem höheren Risiko für nicht-chirurgische und schwere Komplikationen, nicht aber chirurgischer Morbidität ausgesetzt sind. In der Alters-stratifizierten Überlebensanalyse war zu beobachten, dass ältere Patienten mit erhöhtem intraoperativen Blutverlust ein signifikant schlechteres Gesamtüberleben aufwiesen. Unter Anwendung einer erweiterten Regressionsanalyse mit der Möglichkeit der Beschreibung zeitvariierender Variablen-Effekte konnte dargelegt werden, dass adjustiert an prognostisch relevante Störvariablen Komorbiditäten und das Patientenalter innerhalb der ersten 39 postoperativen Monate keinen signifikanten Einfluss auf das Überleben hatten. In einer Subgruppenanalyse der Patienten mit kolorektalen Lebermetastasen wurde der Effekt des Alters erst bei 70 Monaten relevant. Ein Vergleich multivariat adjustierter Hazardkurven mit Sterbetafeln des Statistischen Bundesamts ergab, dass das Sterberisiko älterer Patienten 66

Monate nach Operation relevant abfällt und ein Jahr danach das Niveau der Allgemeinbevölkerung erreicht („*statistical cure*"). Das Patientenalter stellt per se somit keine Kontraindikation gegen eine Leberresektion dar, insbesondere nicht bei Resektion kolorektaler Lebermetastasen. Allerdings sind ältere Patienten bezüglich nicht-chirurgischer Komplikationen sowie unabhängig von ihren Komorbiditen aufgrund Alters-bedingt reduzierter physiologischer Reserven insbesondere durch erhöhten Blutverlust gefährdet.

In einer weiteren Untersuchung wurde die Rolle der perioperativen Erythrozytentransfusion bei Resektion kolorektaler Lebermetastasen untersucht. Im Rahmen der Resektion von Primärtumoren existiert gute Evidenz, dass diese mit einer signifikant früheren Tumorrekurrenz assoziiert ist. Patienten, welche eine Transfusion erhielten, zeigten ein signifikant verkürztes Krankheits-freies Überleben. Auch multivariat adjustiert an den intraoperativen Blutverlust sowie prognostisch relevante Störvariablen zeigte sich die Transfusion als unabhängiger Risikofaktor. Eine Transfusion sollte damit auch aus onkologischen Gesichtspunkten vermieden werden. Eine weitere Arbeit evaluierte die Wertigkeit der Resektion nicht-kolorektaler Lebermetastasen. Patienten mit urogenitalen Tumoren, insbesondere Nierenzellkarzinomen, zeigten sich mit guter Prognose, letztere in einem *Match*-Vergleich mit dem Gesamtüberleben von Patienten mit kolorektalen Lebermetastasen vergleichbar. Schlechteres Überleben zeigte sich für die Gruppe nicht-kolorektaler gastrointestinaler Tumore. Als unabhängige prognostische Variablen wurden eine extrahepatische Tumormanifestation, die Anzahl der Lebermetastasen, die Resektion nicht im Gesunden und das Auftreten postoperativer Komplikationen identifiziert.

In den zur prognostischen Wertigkeit der histomorphologischen und molekularen Phänotypisierung des Papillenkarzinoms in seine Subtypen (intestinaler und pankreatobiliärer Typ) durchgeführten translationalen Arbeiten wurde aufgezeigt, dass diese bisher in der klinischen Routine nicht berücksichtigte Subtypisierung von signifikanter klinischer Relevanz ist. Patienten mit pankreatobiliärem Subtyp zeigten im Vergleich zum intestinalen Typ signifikant fortgeschrittenere Tumorstadien und ein

schlechteres Gesamtüberleben (25 vs. 98 Monate). Der pankreatobiliäre Subtyp wurde ferner als unabhängiger prognostischer Risikofaktor identifiziert. Im Rahmen der molekularen Phänotypisierung der Tumore erwiesen sich MUC2 und CK20 mit dem besten positiv prädiktiven Wert. CK7 zeigte die höchste Sensitivität. Im Hinblick auf den prognostischen Nutzen war die morphologische Klassifikation in der univariaten Überlebens-Analyse am aussagekräftigsten. CK7 und MUC2 erwiesen sich ebenfalls als signifikant prognostische Marker. Patienten mit Tumoren, welche eine pankreatobiliäre Differenzierung aufwiesen und deren Tumore CK7-positiv oder MUC2-negativ waren, waren im Vergleich zur alleinigen morphologischen Subtypisierung mit verschlechtertem Gesamtüberleben assoziiert. Darüber hinaus stellte die Immunphänotypisierung eine Hilfestellung dar, den Anteil der schwierig zu klassifizierenden Tumore weiter einordnen und spezifizieren zu können. In der Analyse konnte ferner beobachtet werden, dass Patienten mit pankreatobiliär differenzierten im Gegensatz zu solchen mit intestinal differenzierten Tumoren von einer adjuvanten Gemcitabine-basierten Chemotherapie zu profitieren scheinen. Bei der Entität des Papillenkarzinoms scheint es sich also nicht um eine homogene Tumorentität zu handeln, als welche sie bisher in der klinischen Routine behandelt wird. Die vorliegenden Ergebnisse weisen auf wichtige Unterschiede in Tumorbiologie und -aggressivität, Tumorcharakteristika, Prognose sowie Chemosensitivität zwischen intestinalem und pankreatobiliärem Subtyp hin.

4. Literatur

Aalen OO (1989) A linear regression model for the analysis of life times Stat Med 8:907-925

Abadi A, Saadat S, Yavari P, Bajdik C, Jalili P (2011) Comparison of Aalen's additive and Cox proportional hazards models for breast cancer survival: analysis of population-based data from British Columbia, Canada Asian Pac J Cancer Prev 12:3113-3116

Acheson AG, Brookes MJ, Spahn DR (2012) Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis Ann Surg 256:235-244 doi:10.1097/SLA.0b013e31825b35d5

Adam R et al. (2010) Liver resection of colorectal metastases in elderly patients Br J Surg 97:366-376 doi:10.1002/bjs.6889

Al-Refaie WB et al. (2010) Major cancer surgery in the elderly: results from the American College of Surgeons National Surgical Quality Improvement Program Ann Surg 251:311-318 doi:10.1097/SLA.0b013e3181b6b04c

Aldrighetti L, Arru M, Caterini R, Finazzi R, Comotti L, Torri G, Ferla G (2003) Impact of advanced age on the outcome of liver resection World J Surg 27:1149-1154 doi:10.1007/s00268-003-7072-y

Amato A, Pescatori M (2006) Perioperative blood transfusions for the recurrence of colorectal cancer Cochrane Database Syst Rev:CD005033 doi:10.1002/14651858.CD005033.pub2

Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, Pawlik TM (2008) Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 12:842-851 doi:10.1007/s11605-008-0494-y

Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O (2000) Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection J Am Coll Surg 191:38-46

Bhatia S, Miller RC, Haddock MG, Donohue JH, Krishnan S (2006) Adjuvant therapy for ampullary carcinomas: the Mayo Clinic experience Int J Radiat Oncol Biol Phys 66:514-519 doi:10.1016/j.ijrobp.2006.04.018

Blajchman MA (2002) Immunomodulation and blood transfusion Am J Ther 9:389-395

Brown RE, Bower MR, Martin RC (2010) Hepatic resection for colorectal liver metastases Surg Clin North Am 90:839-852 doi:10.1016/j.suc.2010.04.012

Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI (2013) Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions Br J Anaesth 110:690-701 doi:10.1093/bja/aet068

Chang CM et al. (2014) Preoperative risk score predicting 90-day mortality after liver resection in a population-based study Medicine (Baltimore) 93:e59 doi:10.1097/MD.0000000000000059

Chang DK et al. (2013) Histomolecular phenotypes and outcome in adenocarcinoma of the ampulla of vater J Clin Oncol 31:1348-1356 doi:10.1200/JCO.2012.46.8868

Cooper GS, Yuan Z, Landefeld CS, Johanson JF, Rimm AA (1995) A national population-based study of incidence of colorectal cancer and age. Implications for screening in older Americans Cancer 75:775-781

Dimick JB, Cowan JA, Jr., Knol JA, Upchurch GR, Jr. (2003) Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database Arch Surg 138:185-191

Erdogan D, Busch OR, Gouma DJ, van Gulik TM (2009) Morbidity and mortality after liver resection for benign and malignant hepatobiliary lesions Liver Int 29:175-180 doi:10.1111/j.1478-3231.2008.01806.x

Fischer HP, Zhou H (2003) [Pathogenesis and histomorphology of ampullary carcinomas and their precursor lesions. Review and individual findings] Pathologe 24:196-203 doi:10.1007/s00292-003-0617-x

Fitzgerald TL, Brinkley J, Banks S, Vohra N, Englert ZP, Zervos EE (2014) The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review Langenbecks Arch Surg 399:989-1000 doi:10.1007/s00423-014-1241-3

Fong Y et al. (1997) Liver resection for colorectal metastases J Clin Oncol 15:938-946 doi:10.1200/jco.1997.15.3.938

Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases Ann Surg 230:309-318; discussion 318-321

Gassler N, Knuchel R (2012) [Tumors of Vater's ampulla] Pathologe 33:17-23 doi:10.1007/s00292-011-1546-8

Ghio M, Contini P, Negrini S, Mazzei C, Zocchi MR, Poggi A (2011) Down regulation of human natural killer cell-mediated cytolysis induced by blood transfusion: role of transforming growth factor-beta(1), soluble Fas ligand, and soluble Class I human leukocyte antigen Transfusion 51:1567-1573 doi:10.1111/j.1537-2995.2010.03000.x

Hamel MB, Henderson WG, Khuri SF, Daley J (2005) Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery J Am Geriatr Soc 53:424-429 doi:10.1111/j.1532-5415.2005.53159.x

Hanazaki K et al. (2001) Hepatic resection for large hepatocellular carcinoma Am J Surg 181:347-353

Howe JR, Klimstra DS, Moccia RD, Conlon KC, Brennan MF (1998) Factors predictive of survival in ampullary carcinoma Ann Surg 228:87-94

Hyder O et al. (2013) A risk model to predict 90-day mortality among patients undergoing hepatic resection J Am Coll Surg 216:1049-1056 doi:10.1016/j.jamcollsurg.2013.01.004

Ijtsma AJ et al. (2008) The survival paradox of elderly patients after major liver resections J Gastrointest Surg 12:2196-2203 doi:10.1007/s11605-008-0563-2

Jarnagin WR et al. (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade Ann Surg 236:397-406; discussion 406-397 doi:10.1097/01.SLA.0000029003.66466.B3

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics CA Cancer J Clin 61:69-90 doi:10.3322/caac.20107

Kim R, Chabot J, Saif MW (2011) Adjuvant treatment for ampullary cancer. Highlights from the "2011 ASCO Annual Meeting". Chicago, IL, USA; June 3-7, 2011 JOP 12:362-363

Kimura W, Futakawa N, Yamagata S, Wada Y, Kuroda A, Muto T, Esaki Y (1994) Different clinicopathologic findings in two histologic types of carcinoma of papilla of Vater Jpn J Cancer Res 85:161-166

Klinkenbijl JH et al. (1999) Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group Ann Surg 230:776-782; discussion 782-774

Krebs in Deutschland 2011/2012, Pressemitteilung. Robert Koch Institut, Berlin; (2015) Vol 10. Berlin

Melloul E, Halkic N, Raptis DA, Tempia A, Demartines N (2012) Right hepatectomy in patients over 70 years of age: an analysis of liver function and outcome World J Surg 36:2161-2170 doi:10.1007/s00268-012-1621-1

Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ (2006) Outcomes after major hepatectomy in elderly patients J Am Coll Surg 203:677-683 doi:10.1016/j.jamcollsurg.2006.07.025

Moggia E, Rouse B, Simillis C, Li T, Vaughan J, Davidson BR, Gurusamy KS (2016) Methods to decrease blood loss during liver resection: a network meta-analysis Cochrane Database Syst Rev 10:CD010683 doi:10.1002/14651858.CD010683.pub3

Motoyama H et al. (2015) Impact of advanced age on the short- and long-term outcomes in patients undergoing hepatectomy for hepatocellular carcinoma: a single-center analysis over a 20-year period Am J Surg 209:733-741 doi:10.1016/j.amjsurg.2014.05.026

Mullen JT et al. (2007) Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy J Am Coll Surg 204:854-862; discussion 862-854 doi:10.1016/j.jamcollsurg.2006.12.032

Neoptolemos JP et al. (2012) Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial JAMA 308:147-156 doi:10.1001/jama.2012.7352

Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie Cancer 77:1254-1262

Nygard IE, Lassen K, Kjaeve J, Revhaug A (2012) Mortality and survival rates after elective hepatic surgery in a low-volume centre are comparable to those of high-volume centres ISRN Surg 2012:783932 doi:10.5402/2012/783932

O'Connell JB, Maggard MA, Manunga J, Jr., Tomlinson JS, Reber HA, Ko CY, Hines OJ (2008) Survival after resection of ampullary carcinoma: a national population-based study Ann Surg Oncol 15:1820-1827 doi:10.1245/s10434-008-9886-1

Petrowsky H, Clavien PA (2005) Should we deny surgery for malignant hepato-pancreatico-biliary tumors to elderly patients? World J Surg 29:1093-1100 doi:10.1007/s00268-005-1130-6

Poston GJ et al. (2005) OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer J Clin Oncol 23:7125-7134 doi:10.1200/JCO.2005.08.722

Pox C et al. (2013) [S3-guideline colorectal cancer version 1.0] Z Gastroenterol 51:753-854 doi:10.1055/s-0033-1350264

Quan D et al. (2012) The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review Surgery 151:860-870 doi:10.1016/j.surg.2011.12.018

Reddy SK et al. (2011) Major liver resection in elderly patients: a multi-institutional analysis J Am Coll Surg 212:787-795 doi:10.1016/j.jamcollsurg.2010.12.048

Schadde E, Schnitzbauer AA, Tschuor C, Raptis DA, Bechstein WO, Clavien PA (2015) Systematic review and meta-analysis of feasibility, safety, and efficacy of a novel procedure: associating liver partition and portal vein ligation for staged hepatectomy Ann Surg Oncol 22:3109-3120 doi:10.1245/s10434-014-4213-5

Scheele J, Altendorf-Hofmann A, Grube T, Hohenberger W, Stangl R, Schmidt K (2001) [Resection of colorectal liver metastases. What prognostic factors determine patient selection?] Chirurg 72:547-560

Scheike TH, Zhang MJ (2003) Extensions and applications of the Cox-Aalen survival model Biometrics 59:1036-1045

Schiergens TS et al. (2015a) Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period Surgery 158:1530-1537 doi:10.1016/j.surg.2015.07.019

Schiergens TS et al. (2016a) Time-dependent impact of age and comorbidities on long-term overall survival after liver resection Liver Int 36:1340-1350 doi:10.1111/liv.13068

Schiergens TS et al. (2016b) Liver Resection for Non-colorectal Non-neuroendocrine Metastases: Where Do We Stand Today Compared to Colorectal Cancer? J Gastrointest Surg 20:1163-1172 doi:10.1007/s11605-016-3115-1

Schiergens TS, Rentsch M, Kasparek MS, Frenes K, Jauch KW, Thasler WE (2015b) Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases Dis Colon Rectum 58:74-82 doi:10.1097/DCR.0000000000000233

Schiergens TS et al. (2015c) Histomorphologic and molecular phenotypes predict gemcitabine response and overall survival in adenocarcinoma of the ampulla of Vater Surgery 158:151-161 doi:10.1016/j.surg.2015.02.001

Schiergens TS, Stielow C, Schreiber S, Hornuss C, Jauch KW, Rentsch M, Thasler WE (2014) Liver resection in the elderly: significance of comorbidities and blood loss J Gastrointest Surg 18:1161-1170 doi:10.1007/s11605-014-2516-2

Schnitzbauer AA et al. (2012) Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings Ann Surg 255:405-414 doi:10.1097/SLA.0b013e31824856f5

Shirabe K et al. (2009) Early outcome following hepatic resection in patients older than 80 years of age World J Surg 33:1927-1932 doi:10.1007/s00268-009-0122-3

Sikora SS, Balachandran P, Dimri K, Rastogi N, Kumar A, Saxena R, Kapoor VK (2005) Adjuvant chemo-radiotherapy in ampullary cancers Eur J Surg Oncol 31:158-163 doi:10.1016/j.ejso.2004.08.013

Simons JP, Hill JS, Ng SC, Shah SA, Zhou Z, Whalen GF, Tseng JF (2009a) Perioperative mortality for management of hepatic neoplasm: a simple risk score Ann Surg 250:929-934 doi:10.1097/SLA.0b013e3181bc9c2f

Simons JP, Ng SC, Hill JS, Shah SA, Bodnari A, Zhou Z, Tseng JF (2009b) In-hospital mortality for liver resection for metastases: a simple risk score J Surg Res 156:21-25 doi:10.1016/j.jss.2009.03.073

Smeenk HG et al. (2007) Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term

results of EORTC trial 40891 Ann Surg 246:734-740 doi:10.1097/SLA.0b013e318156eef3

Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA (2009) Future of cancer incidence in the United States: burdens upon an aging, changing nation J Clin Oncol 27:2758-2765 doi:10.1200/JCO.2008.20.8983

Swanson RS, Pezzi CM, Mallin K, Loomis AM, Winchester DP (2014) The 90-day mortality after pancreatectomy for cancer is double the 30-day mortality: more than 20,000 resections from the national cancer data base Ann Surg Oncol 21:4059-4067 doi:10.1245/s10434-014-4036-4

Turrentine FE, Wang H, Simpson VB, Jones RS (2006) Surgical risk factors, morbidity, and mortality in elderly patients J Am Coll Surg 203:865-877 doi:10.1016/j.jamcollsurg.2006.08.026

Turrini O et al. (2005) [Major hepatectomy for metastasis of colorectal cancer improves survival in the elderly] Ann Chir 130:562-565 doi:10.1016/j.anchir.2005.07.004

Virani S et al. (2007) Morbidity and mortality after liver resection: results of the patient safety in surgery study J Am Coll Surg 204:1284-1292 doi:10.1016/j.jamcollsurg.2007.02.067

Wei AC, Tung-Ping Poon R, Fan ST, Wong J (2003) Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma Br J Surg 90:33-41 doi:10.1002/bjs.4018

Westgaard A, Pomianowska E, Clausen OP, Gladhaug IP (2013) Intestinal-type and pancreatobiliary-type adenocarcinomas: how does ampullary carcinoma differ from other periampullary malignancies? Ann Surg Oncol 20:430-439 doi:10.1245/s10434-012-2603-0

Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA (1998) Periampullary adenocarcinoma: analysis of 5-year survivors Ann Surg 227:821-831

Zacharias T, Jaeck D, Oussoultzoglou E, Bachellier P, Weber JC (2004) First and repeat resection of colorectal liver metastases in elderly patients Ann Surg 240:858-865

5. Originalarbeiten der kumulativen Habilitationsleistung

1) **Schiergens TS,** Lüning J, Renz BW, Thomas M, Pratschke S, Feng H, Lee SM, Engel E, Rentsch M, Guba M, Werner J, Thasler WE. Liver resection for non-colorectal non-neuroendocrine metastases: Where do we stand today compared to colorectal cancer? *J Gastrointest Surg* 2016; 20(6):1163-72.
2) **Schiergens TS,** Lindenthaler A, Thomas MN, Rentsch M, Mittermeier L, Brand K, Küchenhoff H, Lee S, Guba M, Werner J, Thasler WE; Time-dependent impact of age and co-morbidities on long-term overall survival after liver resection. *Liver Int* 2016; 36(9):1340-50.
3) **Schiergens TS,** Dörsch M, Mittermeier L, Brand K, Küchenhoff H, Lee SM, Feng H, Jauch KW, Werner J, Thasler WE; Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period. *Surgery* 2015; 158(6):1530-7.
4) **Schiergens TS,** Reu S, Neumann J, Renz BW, Niess H, Boeck S, Heinemann V, Bruns CJ, Jauch KW, Kleespies A; Histomorphologic and molecular phenotypes predict gemcitabine response and overall survival in adenocarcinoma of the ampulla of Vater; *Surgery* 2015; 158(1):151-61.
5) **Schiergens TS,** Rentsch M, Kasparek MS, Frenes K, Jauch KW, Thasler WE; Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases; *Dis Colon Rectum* 2015; 58(1):74-82.
6) **Schiergens TS,** Stielow C, Schreiber S, Hornuss C, Jauch KW, Rentsch M, Thasler WE; Liver resection in the elderly: significance of comorbidities and blood loss. *J Gastrointest Surg* 2014; 18(6):1161-70.

J Gastrointest Surg (2016) 20:1163–1172
DOI 10.1007/s11605-016-3115-1

ORIGINAL ARTICLE

Liver Resection for Non-colorectal Non-neuroendocrine Metastases: Where Do We Stand Today Compared to Colorectal Cancer?

Tobias S. Schiergens[1] · Juliane Lüning[1] · Bernhard W. Renz[1] · Michael Thomas[1] · Sebastian Pratschke[1] · Hao Feng[1] · Serene M. L. Lee[1] · Jutta Engel[2] · Markus Rentsch[1] · Markus Guba[1] · Jens Werner[1] · Wolfgang E. Thasler[1]

Received: 1 December 2015 / Accepted: 16 February 2016 / Published online: 26 February 2016

Abstract The continuing controversy about surgery for non-colorectal non-neuroendocrine liver metastases (NCRNNE) necessitates identifying risk factors of worsened outcomes to improve patient selection and survival. Prospectively collected data of 167 patients undergoing hepatectomy for NCRNNE were analyzed, and a comparison to a matched population of colorectal liver metastases (CLM) was performed. Overall survival (OS) (35 vs. 54 months; $P=0.008$) and recurrence-free survival (RFS) (15 vs. 29 months; $P=0.004$) of NCRNNE patients were significantly shorter compared to those with CLM. The best survival was found in the genitourinary (GU; OS, 45 months; RFS, 21 months) NCRNNE subgroup, whereas survival for gastrointestinal (GI) metastases was low (OS, 8 months; RFS, 7 months). Patients with renal cell carcinoma (RCC) showed excellent outcomes when compared to CLM (OS, 50 vs. 51 months; $P=0.901$). Extrahepatic disease (EHD) was identified as independent prognostic factor for reducing both RFS ($P=0.040$) and OS ($P=0.046$). The number of liver lesions ($P=0.024$), residual tumor ($P=0.025$), and major complications ($P=0.048$) independently diminished OS. The degree of survival advantage by surgery is determined by the primary tumor site, EHD, the number of metastases, and residual tumor. Thus—even more than in CLM—these oncological selection criteria must prevail. GU metastases, especially RCC, represent a favorable subgroup.

Keywords Liver resection · Metastasis · Non-colorectal · Non-neuroendocrine · Renal cell carcinoma

Introduction

Liver resection for metastatic cancer has become standard care for selected patients.[1] The role of hepatectomy for colorectal liver metastases (CLM) has been shown to be safe and oncologically effective extending survival and improving quality of life.[2–4] Furthermore, resection for hepatic metastases of neuroendocrine tumors is widely accepted with the objective of symptom control as well as improving survival, and the excellent long-term outcome of those patients has been demonstrated.[5,6] For non-colorectal, non-neuroendocrine liver metastases (NCRNNE), however, the significance of surgery has not been satisfactorily elucidated, especially regarding long-term outcome and the comparison to CLM. In the era of improved periprocedural outcomes with low rates of morbidity and mortality, there is increasing evidence for its safety and oncological benefit.[7,8] Patients being selected for resection of NCRNNE, however, represent a heterogeneous cohort with a broad range of outcomes and a highly selected population of subjects with metastatic cancer. Thus, there are still some controversies concerning the oncological value of liver surgery in these patients. A legitimate aspect calling resection into question is that metastatic liver disease of solid tumors other than colorectal cancer is even more considered as advanced and systemic disease entailing unfavorable outcomes. Furthermore, most published series report retrospective data

✉ Tobias S. Schiergens
Tobias.Schiergens@med.uni-muenchen.de

[1] Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Hospital of the University of Munich, Marchioninistr. 15, 81377 Munich, Germany

[2] Munich Cancer Registry (MCR) of the Munich Tumor Center (TZM), Institute for Medical Information Sciences, Biometry, and Epidemiology (IBE), University Hospital of Munich, Munich, Germany

of only a small number of patients with short follow-ups (reviewed in [8]). In addition, many series are subject to secular trends displaying time spans back in the 1980s.[8] Thus, identifying prognostic factors enabling an improved and tailored patient selection are of the surgeon's utmost concern. Long-term follow-up, identification of independent prognostic factors, stratification by primary tumor site, and comparison to CLM might therefore help to gain a better understanding of the long-term efficacy of NCRNNE resection.

Thus, this study aimed to analyze long-term recurrence-free (RFS) and overall survival (OS) of prospectively assessed patients undergoing liver surgery for NCRNNE and to compare this population to a matched cohort of CLM patients.

Materials and Methods

Design and Study Population

Prospectively collected demographic, clinical, laboratory, and perioperative data as well as RFS and OS of patients undergoing elective hepatectomy for NCRNNE and CLM between 2003 and 2013 at our institution were retrospectively analyzed. For the comparison to CLM, patients were selected matching for patient age (±5 years), gender, date of surgery (±5 years), extent of liver resection, synchronous vs. metachronous incidence of metastases, and comorbidities encoded by the Charlson comorbidity index (CCI).[9] Patient records and information was anonymized and de-identified prior to analysis. Design, data acquisition, statistical methods, and manuscript preparation were carried out according to STROBE guidelines for strengthening of reporting of observational studies.[10]

Data Collection

For prospective, standardized data assessment, electronic case report forms (eCRF) were used as previously reported.[11] Primary tumor site (PTS) was stratified into the well-established subgroups of genitourinary (GU), gastrointestinal (GI), soft tissue (ST), breast (BRE), melanoma (MEL), and miscellaneous (MISC) tumors. Comorbidities were stratified by applying the classifications of the American Association of Anesthesiologists (ASA) and the CCI.[9] Major liver resection was defined as hemi-hepatectomy or extended hemi-hepatectomy. Extended resection was defined as resection of at least one further organ. Major estimated blood loss (EBL) was defined as >1000 mL. Postoperative morbidity was assessed according to the validated Clavien-Dindo classification (CD).[12] Synchronous disease was defined as metastases being diagnosed within 6 months after diagnosis of the primary tumor.[13] Survival was determined from the date of initial surgery to the date of either biopsy-proven or radiologic evidence of disease recurrence or progression (RFS) or to the date of death or last recall (OS). Additionally, post-progression survival of UICC stage IV patients was obtained from the local cancer registry.[14]

Statistical Analysis

Results were expressed as mean values ± standard deviation (SD) or median and range [minimum and maximum]. For comparison of frequencies, X^2 test or Fisher's exact test (cases of low frequency) were used where appropriate. Univariate survival analysis (RFS, OS) was performed by the Kaplan-Meier method applying the log-rank test for statistical discrimination. For continuous variables, a Cox regression model was calculated assessing one continuous variable for survival. For multivariate modeling of RFS and OS, Cox's proportional hazard model was calculated by subsequently entering factors that showed significant univariate association and which were therefore medically and statistically hypothesized for adjustment. In case of multivariate analysis of survival, the hazard ratio (HR) with its 95 % confidence interval (95 % CI) was calculated for binary predictors. Statistical analyses were based on two-tailed calculations regarding $P < 0.05$ as statistically significant. For statistical analysis, SPSS statistical software package (version 22.0, IBM, Chicago, Ill) and Prism (version 3.0, GraphPad, La Jolla, CA) were used.

Results

Study Population and Primary Tumor Sites

One hundred and sixty-seven patients who underwent liver resection for NCRNNE between 2003 and 2013 were included in the present study. For comparison, 167 patients undergoing resection for CLM within the same time period and meeting the matching criteria (1:1) were identified. The PTS and the clinical characteristics of the study population are shown in Table 1. Across the entire NCRNNE cohort, GU ($N=61$; 36 %) and GI malignancies ($N=43$; 26 %) were the most frequent PTS. Twenty-five patients (15 %) had soft tissue tumors, 16 (10 %) breast cancer, and 8 (5 %) melanoma. The most frequent tumor entities are displayed in Table 2. Among the 14 patients with miscellaneous tumors, four subjects with head and neck cancer, three with metastases of unknown primary (CUP), two with thyroid carcinomas, two with lymphoma, two with non-small cell lung cancer (NSCLC), and one with adrenal gland cancer were found.

Table 1 Baseline characteristics of the NCRNNE study population according to the primary tumor site

	All *N* (%)	GU *N* (%)	GI *N* (%)	ST *N* (%)	BRE *N* (%)	MEL *N* (%)	MISC *N* (%)
Patient number	167 (100)	61 (36)	43 (26)	25 (15)	16 (10)	8 (5)	14 (8)
Age	60 [18–86]	63 [26–82]	64 [32–83]	60 [18–73]	54 [38–77]	54 [30–75]	61 [34–86]
Gender (female)	101 (61)	40 (66)	20 (47)	16 (64)	16 (100)	4 (50)	5 (36)
ASA[a] >grade 2	109 (65)	41 (67)	26 (60)	15 (60)	12 (75)	4 (50)	11 (79)
CCI[b]	6.47 ± 0.81	6.41 ± 0.80	6.56 ± 0.76	6.48 ± 0.87	6.38 ± 0.71	6.25 ± 0.46	6.71 ± 1.01
>3 liver metastases	16 (10)	4 (7)	7 (16)	1 (4)	1 (6)	1 (13)	2 (14)
Largest diameter ≥50 mm	40 (24)	17 (28)	5 (12)	9 (36)	4 (25)	3 (38)	2 (14)
Synchronous[c]	73 (44)	21 (34)	30 (70)	10 (40)	2 (13)	0 (0)	10 (71)
Extrahepatic disease	47 (28)	17 (28)	12 (28)	7 (28)	3 (19)	2 (25)	3 (21)
Previous chemotherapy	68 (41)	26 (43)	16 (37)	8 (32)	15 (94)	2 (25)	1 (7)
Multimodal treatment	128 (77)	47 (77)	36 (84)	17 (68)	16 (100)	4 (50)	8 (57)
R0 resection	143 (86)	57 (93)	33 (77)	20 (80)	13 (81)	7 (9)	13 (93)
Major hepatectomy	51 (31)	19 (31)	6 (14)	11 (44)	8 (50)	5 (63)	2 (14)
Extended resection	61 (37)	22 (36)	24 (56)	13 (52)	0 (0)	0 (0)	2 (14)
Laparoscopic resection	12 (7)	4 (7)	5 (12)	0 (0)	3 (19)	0 (0)	0 (0)
Major EBL[d]	44 (26)	19 (31)	9 (21)	9 (36)	2 (13)	3 (38)	2 (14)
Perioperative transfusion	72 (43)	32 (52)	18 (42)	12 (48)	3 (19)	3 (38)	4 (29)
Major morbidity (CD[e] >2)	41 (25)	19 (31)	12 (28)	8 (32)	1 (7)	0 (0)	1 (7)
In-hospital mortality	8 (5)	3 (5)	2 (5)	2 (8)	0 (0)	0 (0)	1 (7)
Median follow-up [months]	29	37	7	44	29	35	23
Median RFS[f] [months]	15	21	7	22	14	18	12
Median OS[g] [months]	35	45	8	46	32	29	31
1-year OS [%]	71.8	78.1	44.2	63.1	81.3	87.5	63.5
3-year OS [%]	49.0	57.2	29.2	52.1	35.7	37.5	34.7

GU genitourinary, *GI* gastrointestinal, *ST* soft tissue, *BRE* breast, *MEL* melanoma, *MISC* miscellaneous

[a] American Society of Anaesthesiologists

[b] Charlson comorbidity index

[c] Being assessed within 6 months after primary tumor diagnosis

[d] Estimated blood loss

[e] Clavien-Dindo

[f] Recurrence-free survival

[g] Overall survival

Clinical Characteristics

The clinical baseline and perioperative characteristics stratified by PTS are summarized in Table 1. Altogether, the median age was 60 years [18–86]. The median follow-up was 29 months. The female gender preponderated in GU, ST, and BRE cancers, while the gender ratio was balanced in the GI and MEL group. Besides GI lesions (30 %), NCRNNE were more frequently resected as metachronous metastases (56 % overall). Nearly one-third of all the patients had extrahepatic disease (EHD) with an even distribution over the subgroups. Five patients had EHD as a limited peritoneal carcinosis which had not been evident before surgery, and resection was pursued regardless as an individual decision. Forty-one percent had preoperative chemotherapy, and 47 % were planned to receive adjuvant chemotherapy. Overall, in 128 patients (77 %), liver resection for NCRNNE was embedded within multimodality treatment.

Survival

RFS and OS of all NCRNNE patients and stratified by PTS are displayed in Tables 1 and 2. Table 2 also shows the post-progression survival of all UICC stage IV patients of the respective entity. Kaplan-Meier estimators of the study population are illustrated in Fig. 1. The median OS and RFS of all the NCRNNE patients were 35 and 15 months, respectively. The best survival rates were found for the GU (OS, 45 months;

Table 2 Primary tumor sites with recurrence-free (RFS) and overall survival (OS) as well as survival from all stage IV patients with the respective tumor (data from the local cancer registry)

Primary tumor site	*N* (%)	Median RFS (months)	Median OS (months)	3-year survival (%)	3-year survival all stage IV patients[a] % (*N*)
Genitourinary	61 (36)	21	45		
Kidney	28 (17)	21	50	68	27 (1485)
Ovary	24 (14)	15	33	43	23 (1421)
Uterus	6 (4)	33	33	50	19 (676)
Testis	3 (2)	52	52	50	81 (315)
Gastrointestinal	43 (26)	7	8		
Pancreas	19 (11)	6	7	17	4 (2590)
Stomach	14 (8)	6	15	36	6 (2677)
Peritoneum	6 (4)	31	38	50	N/A
Periampullary	3 (2)	13	13	0	N/A
Soft tissue	25 (15)	22	46		
Sarcoma	17 (10)	22	40	53	20 (541)
GIST	8 (5)	27	50	75	N/A
Breast	16 (10)	14	32	43	34 (6535)
Melanoma	8 (5)	18	29	50	27 (1163)
Uveal	6 (4)	15	24	33	N/A
Skin	2 (1)	18	66	50	N/A

[a] Survival data from all UICC stage IV patients from the local cancer registry (post-progression survival with distant metastases)

RFS, 21 months) and ST subgroup of patients (OS, 46 months; RFS, 22 months) followed by BRE (OS, 32 months; RFS, 14 months) and MEL (OS, 29 months; RFS, 18 months). Among GU patients, those with renal cell carcinoma (RCC) showed excellent median OS (50 months) and RFS (21 months). The median survival for GI metastases was low, indeed (OS, 8 months; RFS, 7 months), and this was the only subgroup with significant shortened OS when compared to the rest of the NCRNNE population ($P=0.004$). However, 3-year survival rates of 29 % were found with a relevant rate of long-term survivors.

Comparison to Colorectal Liver Metastases

Besides the abovementioned matching criteria, no other significant differences in baseline and perioperative characteristics were found between the NCRNNE and CLM patients. Of note, one-fourth ($N=41$) of the NCRNNE patients experienced major postoperative complications which was comparable to the matched CLM population ($N=44$, 26 %; $P=0.802$). The Kaplan-Meier estimators of the NCRNNE compared to the matched CLM population are shown in Fig. 2a, b. OS and RFS of the NCRNNE patients were significantly shorter (OS, 35 vs. 54 months, $P=0.008$; RFS, 15 vs. 29 months, $P=0.004$). Comparison of RCC patients to its separately matched CLM population revealed comparable survival rates (OS, 50 vs. 51 months; $P=0.901$; Fig. 2c). RFS, however, tended to be worse in RCC (21 vs. 31 months; $P=0.051$; Fig. 2d). Within postoperative hospital stay, eight patients (5 %) died, which did not differ from in-house mortality of CLM patients ($N=6$, 4 %; $P=0.781$).

Univariate and Multivariate Survival Analysis

The univariate survival analysis for OS and RFS is presented in Table 3. The final multivariate regression models are shown in Table 4. EHD was identified as independent prognostic factor for reducing both RFS ($P=0.040$; HR 1.51, 95 % CI 1.02–2.24) and OS ($P=0.046$; HR 1.56, 95 % CI 1.01–2.40). Additionally, the presence of more than three liver lesions ($P=0.024$; HR 1.90, 95 % CI 1.09–3.32), R1 or R2 resection ($P=0.025$; HR 1.82, 95 % CI 1.08–3.05), and the incidence of major postoperative complications ($P=0.048$; HR 1.53, 95 % CI 1.01–2.34) independently diminished OS.

Discussion

We show that liver resection for NCRNNE can be carried out with morbidity and mortality rates that are comparable to those of the CLM patients. Excellent outcomes for the GU and ST patients as well as good survival in the BRE and MEL patients are demonstrated. Survival of patients undergoing surgery for GI metastases is low; however, there is a considerable number of patients with long-term survival. Although the outcome of surgery for CLM is still better, some subgroups such as patients with RCC achieve a comparable long-term outcome. EHD was identified as independent

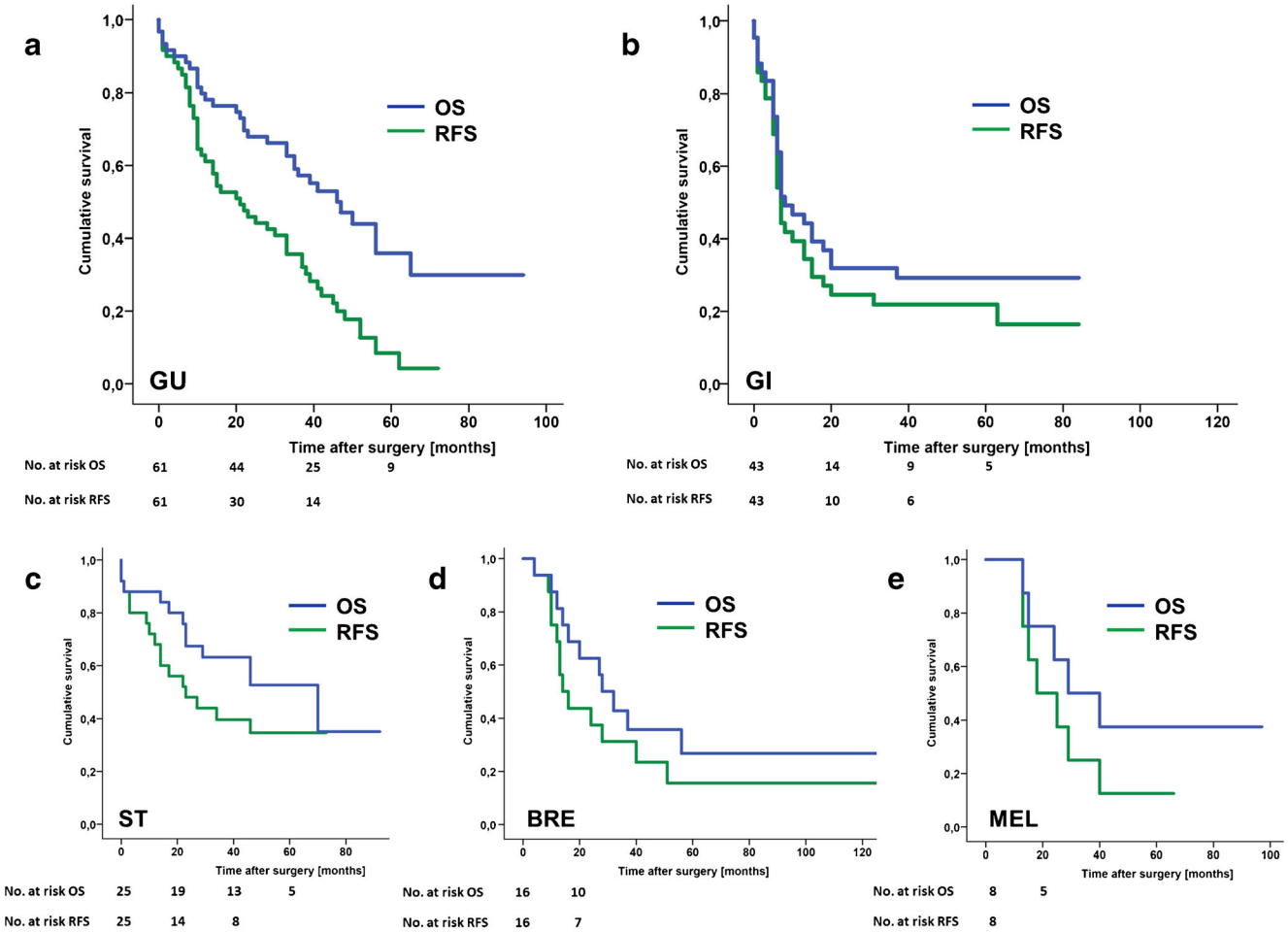


Fig. 1 Overall survival (OS) and recurrence-free survival (RFS) of patients undergoing liver resection for non-colorectal non-neuroendocrine liver metastases (NCRNNE) stratified into subgroups of primary tumor site. Median OS and RFS were 45 and 21 months for genitourinary tumors (GU) (**a**), 8 and 7 months for gastrointestinal tumors (GI) (**b**), 46 and 22 months for soft tissue tumors (ST) (**c**), 32 and 14 months for breast cancer (BRE) (**d**), and 29 and 18 months for melanoma (MEL) (**e**), respectively

prognostic factor for reducing both RFS and OS. In addition, OS was independently shortened by the presence of more than three liver metastases, residual tumor (R1/R2), and by the occurrence of major postoperative complications.

Recent advances in liver surgery, improved perioperative care enabling reduced morbidity and mortality, as well as excellent long-term results of liver resection of CLM have encouraged an increasingly aggressive approach in the surgery of NCRNNE over the last years.[8,15] The rationale behind is that most cancer-related mortality is caused by metastatic disease and the liver is a common metastatic site not only in colorectal but also NCRNNE malignancies.[16] Despite a certain evidence, there is still a lack of detailed knowledge which patients will mostly benefit.[8,17] As corroborated by the current study the prognosis of the NCRNNE patients is still poorer than that of the CLM patients which might be attributed to differences in tumor biology and the availability of effective chemotherapies as well as multimodal concepts. Thus, a thorough approach in patient selection has been suggested considering the individual oncological situation as well as comorbidities.[18] In this context, depending on the PTS, non-surgical therapies do not result in satisfactory outcomes in many entities.

The current study underlines that with regard to NCRNNE, the primary tumor site[8,18] and oncological variables such as the prevalence of EHD, the number of liver metastases, and residual tumor dominantly determine the patient's prognosis. Thus, even more than in CLM[19] or primary liver tumors,[11] oncological selection criteria must prevail in the view of progressive liberalization in NCRNNE patient selection. Extrahepatic tumor manifestation independently reduced both RFS and OS. This might be explained by the diminished ability to control systemic disease in a variety of NCRNNE primary tumors in contrast to colorectal cancer. Thus, the current study calls resection of NCRNNE with EHD into question and suggests the thorough exclusion of EHD prior to surgery. For this purpose, depending on the tumor type, MRI or PET-CT were suggested.[16,18] Although reports have shown that EHD

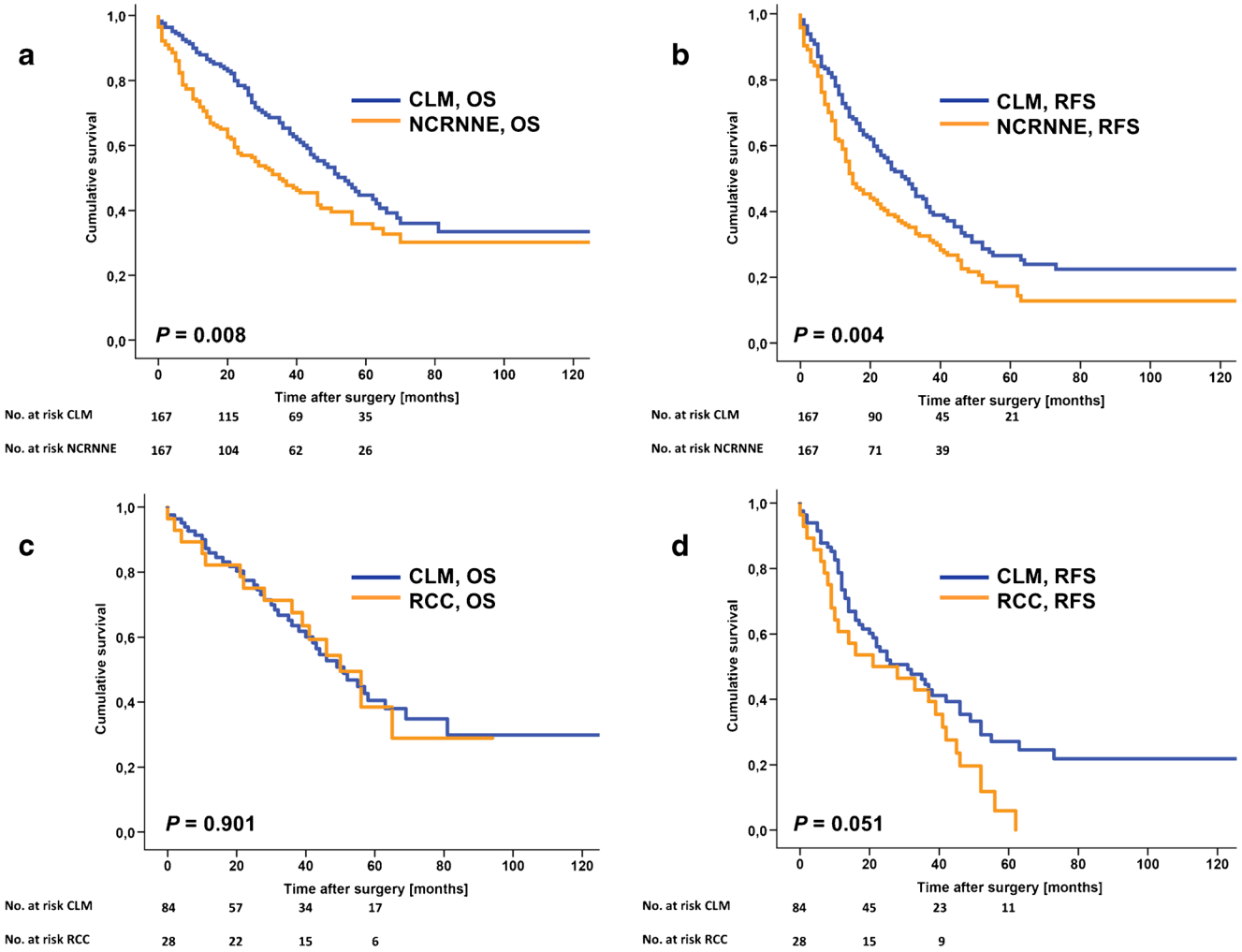


Fig. 2 Overall survival (OS; **a**) and recurrence-free survival (RFS; **b**) of the entire cohort of 167 patients undergoing liver resection for non-colorectal non-neuroendocrine liver metastases (NCRNNE) compared to a matched (1:1) population of patients being resected for colorectal liver metastases (CLM). The median OS of NCRNNE was 35 months compared to 54 months in CLM patients ($P = 0.008$). RFS was also significant shorter in NCRNNE compared to CLM (15 vs. 29 months; $P = 0.004$). Comparison of survival of 28 patients undergoing liver resection for renal cell carcinoma (RCC) compared to a separately matched population of 84 (3:1) patients with colorectal cancer (CLM). While overall survival (OS; **c**) did not differ between RCC and CLM (50 vs. 51 months; $P = 0.901$), recurrence-free survival (RFS; **d**) tended to be worse in RCC (21 vs. 31 months; $P = 0.051$)

does not have a significant impact on survival,[20,21] others[16,22] and the current study found it to relevantly deteriorate the patient's outcome. Furthermore, our data underline that residual tumor should be diligently avoided as it severely deteriorates the patient's prognosis.[20,23] Patients who are unlikely to achieve an R0 resection should be even more carefully selected. Worse impact has also been shown for the number of liver lesions.[16]

Regarding the PTS, GU, BRE, and ST tumors have been described with a favorable prognosis.[16,18,20,23–27] This was also shown by the current analysis. On the other hand, the present study and others[18,27–31] have demonstrated that NCRNNE resection of GI tumors is associated with markedly worse survival. However, this is not the case for metastatic gastrointestinal stromal tumors (GIST; OS, 50 months; RFS, 27 months). The poor outcome of GI metastases was underlined by a recent review calculating the median OS of GU, BRE, and GI subgroups. In this publication, GU metastases were identified as those with the longest expected OS of 63 months with a fairly wide range from 5 to 142 months.[8]

Our work has also identified GU as the subgroup with the best long-term outcome. Among these, the RCC patients were shown to have a comparable long-term prognosis as the CLM patients. In the aforementioned review, eight RCC studies were identified with an expected median OS of 68 months[8] which was better compared to our RCC subgroup (50 months). This might be mainly due to differences in patient characteristics and selection. Staehler et al. reported excellent survival in RCC patients with liver metastases undergoing surgery compared to patients denying surgery and receiving non-

Table 3 Univariate analysis for recurrence-free (RFS) and overall survival (OS)

	RFS *P* value	OS *P* value
Age >70 years	0.137	0.468
Age (continuous)	0.693	0.069
Gender	0.630	0.616
ASA[a] >2	0.156	0.183
CCI[b] >6	0.566	0.178
Previous chemotherapy	0.636	0.250
>3 liver metastases	0.020	0.004
Largest diameter ≥50 mm	0.282	0.630
Synchronous metastases[c]	0.254	0.113
Extrahepatic disease	0.017	0.005
Other major surgery	0.205	0.105
Major hepatectomy	0.698	0.414
Major EBL[d]	0.508	0.931
Perioperative transfusion	0.582	0.626
Residual tumor (R1/R2)	0.134	0.008
Major morbidity (CD[e] >2)	0.167	0.020
GU	0.817	0.189
GI	0.057	0.004
ST	0.112	0.130
BR	0.764	0.810
MEL	0.772	0.723

ASA American Society of Anaesthesiologists, *CCI* Charlson comorbidity index, *EBL* estimated blood loss, *CD* Clavien-Dindo, *GU* genitourinary, *GI* gastrointestinal, *ST* soft tissue, *BRE* breast, *MEL* melanoma, *MISC* miscellaneous

[a] American Society of Anaesthesiologists

[b] Charlson comorbidity index

[c] Being assessed within 6 months after primary tumor diagnosis

[d] Estimated blood loss

[e] Clavien-Dindo

Table 4 Multivariate analysis for recurrence-free (RFS) and overall survival (OS)

	Recurrence-free survival		
	P value	Hazard ratio	95 % CI
>3 liver metastases	0.062	1.66	0.98–2.81
Extrahepatic disease	0.040	1.51	1.02–2.24
Residual tumor (R1/R2)	0.163	1.40	0.87–2.24
	Overall Survival		
	P value	Hazard ratio	95 % CI
>3 liver metastases	0.024	1.90	1.09–3.32
Extrahepatic disease	0.046	1.56	1.01–2.40
Residual tumor (R1/R2)	0.025	1.82	1.08–3.05
Major complications	0.048	1.53	1.01–2.34

surgical therapy (142 vs. 27 months) emphasizing that liver resection is able to prolong survival.[32] Three-year survival was also superior to that of all RCC stage IV patients (68 vs. 27 %); however, this has to be interpreted with caution as these groups may differ in relevant characteristics biasing the outcome. Overall, the data justify an aggressive surgical approach in these patients, and there seems to be a certain consensus about this in the literature.[8,24,32] Patients with testicular cancer had also good survival in the current study (OS and RFS, 52 months). However, although survival is excellent in this subgroup, hepatectomy should be reserved for patients with poor prognosis that have a medically refractory disease.[8,33] In some subgroups such as patients with ovarian cancer and visceral metastases or those with metastatic uterine cancer (EHD), poor outcomes have been reported, and one should be reserved concerning surgery.[8] Our results (Table 2), however, show that in highly selected patients, surgery may be considered in the light of the poor survival in non-surgical patients of less than one year.[34]

Many studies exist reporting on outcomes after resection of liver metastases from breast cancer. Overall, survival after liver surgery seems to be better than one would expect with observation (Table 2, [8]). Comparative studies found improved survival in the surgical group compared to standard medical treatment,[35,36] and the present study also demonstrates good median OS of 32 months. Thus, outcomes after surgery seem to clearly superior to non-surgical therapy (survival of 6 to 14 months, reviewed in [37]).

Worse outcome following resection of non-colorectal non-GIST GI metastases admonishes the surgeon for a strict patient selection. However, the rationale for surgery may be that resection of isolated liver metastases represents a setting of curative intention as the liver may be the only metastatic site according to the portal venous drainage hypothesis. Resection was thwarted by a recent case-control trial that revealed no difference between observation and surgery,[38] and multiple reports demonstrate that this subgroup of NCRNNE is the one having the poorest outcome.[8,18,27–29,39] For this NCRNNE category, an expected median OS of 22 months was calculated including data of 31 cohorts.[8] Outcome after resection for liver metastases of pancreatic cancer was shown to be poor (13 and 20 months, respectively),[40,41] and this is in line with our results of 7 months. For gastric cancer, a median survival of 15 months was shown in the present analysis. Survival advantage for resection has been demonstrated by reports from Japan.[37,40,42,43] However, whenever EHD is present, palliative chemotherapy offers a survival benefit compared to surgery.[44] In our cohort, there was a relevant number of non-colorectal GI patients with long-term survival (Table 2). This indicates that the application of improved selection criteria might result in better outcomes after surgery. Thus, surgery in this most highly selected group, especially in

patients with pancreatic cancer, must be thoroughly weighted against perioperative risks and the potential efficacy and risks of available systemic therapies.

Hepatic metastasectomy for soft tissue tumors was shown to be safe and effective in the current study. Patients with GIST metastases had a median RFS and OS of 27 and 50 months, and sarcoma patients of 22 and 40 months, respectively. The hepatic recurrence rate was shown to be high, but recurrent disease seems to be effectively treated by repeated liver resection.[44] In the absence of highly effective chemotherapies, resection seems to be the only reasonable strategy whenever possible. In a review by Dematteo et al., outcomes of 331 patients with liver metastases of sarcomas were reported. Five-year survival of patients with R0 resection was 30 % compared to 4 % in patients without liver resection.[45] In our study, 3-year survival was 53 % compared to 20 % in all the stage IV patients.

In the present study, survival of 29 (median OS) and 18 (median RFS) months with a 5-year survival rate of 29 % in MEL patients was found. In all other studies that included non-surgical comparator groups, improved survival after liver resection was observed (reviewed in [46]). With non-surgical therapy, survival ranged from 3 to 12 months in patients with uveal melanoma, and it was 6 months in those with cutaneous melanoma.[46] In the light of the survival in the current study (Table 2), metastasectomy seems to be justified. In another study by Martel et al., 11 MEL patients were assessed following liver resection with even better outcomes (median OS of 100 months, 5-year survival of 66 %).[18] Adam et al. found 5-year survival rates of 21 % which is more in line with our results.[40]

Some limitations of the present studies have to be noted and indicate the interpretation of the results with caution. The analysis of a single-center cohort reflects the unique result of a patient population that might not be entirely comparable to other published populations. Survival is determined with regard to varying intervals between diagnosis of the primary tumor and the incidence of metastatic disease.[29] Generalizability may be further hindered by differences in patient characteristics and recent improvements in surgical techniques as well as chemotherapeutic and biologic therapies. Furthermore, patient selection may vary between different centers.[8] NCRNNE patients commonly are treated multidisciplinary, and many receive systemic therapies and/or radiation in tertiary centers. The availability of those complex multimodal strategies could further determine the patient's prognosis.

In addition, comparative outcomes of patients receiving systemic therapy alone were not included in the current study. The comparison to all the stage IV patients is biased by differences in oncologically relevant characteristics. This hinders to make definitive statements of the effectiveness of surgery. Although the current study includes one of the largest single-center cohorts, subgroups stratified by PTS are quite small. As randomized controlled trials are not practical because of the heterogeneity of cancer types and the prevalence of metastases meeting the resection criteria, international multicenter registries are needed. These could provide pooled and therefore more homogeneous data with more emerging trends from which stronger conclusions and more generalizable recommendations regarding patient selection could be made.

Conclusions

In patients undergoing liver resection for NCRNNE, oncological selection criteria must prevail even more than in CLM or primary liver tumors. The degree of survival advantage by surgery seems to be mainly determined by the primary tumor site, the number of liver metastases, and residual tumor. Patient selection should adhere to these variables. In the presence of extrahepatic tumor manifestation, surgery must be an exception based on the individual case. For GU tumors, especially RCC and testicular cancer, the best survival was shown in contrast to non-colorectal GI tumors. For the latter, improved selection criteria must be identified in future trials as surgery has to be thoroughly weighted against perioperative risks and the potential efficacy and risks of available systemic therapies.

Acknowledgments The authors thank Stephanie Schreiber, Dr. Carsta Stielow, and Dr. Hans-Martin Hornung for their dedicated work with the patients' data collection and IT administration of the liver database.

Compliance with Ethical Standards The study was approved by the ethics committee, Faculty of Medicine, Ludwig-Maximilians-University (LMU), Munich, Germany.

Conflict of Interest The authors declare that they have no conflicts of interest.

Financial Support No funding was received for the present study.
This article is not based on a previous communication to a society or meeting.

References

1. Cordera F, Rea DJ, Rodriguez-Davalos M, Hoskin TL, Nagorney DM, Que FG. Hepatic resection for noncolorectal, nonneuroendocrine metastases. J Gastrointest Surg 2005;9:1361–1370.
2. Brown RE, Bower MR, Martin RC. Hepatic resection for colorectal liver metastases. Surg Clin North Am 2010;90:839–852.
3. Quan D, Gallinger S, Nhan C, Auer RA, Biagi JJ, Fletcher GG, Law CH, Moulton CA, Ruo L, Wei AC, McLeod RS. The role of liver resection for colorectal cancer metastases in an era of

multimodality treatment: a systematic review. Surgery 2012;151: 860–870.
4. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 1997;84: 1136–1140.
5. Sutcliffe R, Maguire D, Ramage J, Rela M, Heaton N. Management of neuroendocrine liver metastases. Am J Surg 2004;187:39–46.
6. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003;197:29–37.
7. O'Rourke TR, Tekkis P, Yeung S, Fawcett J, Lynch S, Strong R, Wall D, John TG, Welsh F, Rees M. Long-term results of liver resection for non-colorectal, non-neuroendocrine metastases. Ann Surg Oncol 2008;15:207–218.
8. Fitzgerald TL, Brinkley J, Banks S, Vohra N, Englert ZP, Zervos EE. The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review. Langenbecks Arch Surg 2014;399:989–1000.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370: 1453–1457.
11. Schiergens TS, Stielow C, Schreiber S, Hornuss C, Jauch KW, Rentsch M, Thasler WE. Liver resection in the elderly: significance of comorbidities and blood loss. J Gastrointest Surg 2014;18:1161–1170.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.
13. Mekenkamp LJ, Koopman M, Teerenstra S, van Krieken JH, Mol L, Nagtegaal ID, Punt CJ. Clinicopathological features and outcome in advanced colorectal cancer patients with synchronous vs metachronous metastases. Br J Cancer 2010;103:159–164.
14. Munich Cancer Registry, Munich Tumor Center, 2016. http://www.tumorregister-muenchen.de/en/facts/specific_analysis.php
15. Virani S, Michaelson JS, Hutter MM, Lancaster RT, Warshaw AL, Henderson WG, Khuri SF, Tanabe KK. Morbidity and mortality after liver resection: results of the patient safety in surgery study. J Am Coll Surg 2007;204:1284–1292.
16. Reddy SK, Barbas AS, Marroquin CE, Morse MA, Kuo PC, Clary BM. Resection of noncolorectal nonneuroendocrine liver metastases: a comparative analysis. J Am Coll Surg 2007;204:372–382.
17. Jauch KW, Thasler WE. How safe and effective is hepatic resection for patients with noncolorectal nonendocrine liver metastasis? Nat Clin Pract Gastroenterol Hepatol 2007;4:310–311.
18. Martel G, Hawel J, Rekman J, Croome KP, Bertens K, Balaa FK, Hernandez-Alejandro R. Liver resection for non-colorectal, non-carcinoid, non-sarcoma metastases: a multicenter study. PLoS One 2015;10:e0120569.
19. Schiergens TS, Rentsch M, Kasparek MS, Frenes K, Jauch KW, Thasler WE. Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases. Dis Colon Rectum 2015;58:74–82.
20. Harrison LE, Brennan MF, Newman E, Fortner JG, Picardo A, Blumgart LH, Fong Y. Hepatic resection for noncolorectal, nonneuroendocrine metastases: a fifteen-year experience with ninety-six patients. Surgery 1997;121:625–632.
21. Lang H, Nussbaum KT, Weimann A, Raab R. Liver resection for non-colorectal, non-neuroendocrine hepatic metastases. Chirurg 1999;70:439–446.
22. Yedibela S, Gohl J, Graz V, Pfaffenberger MK, Merkel S, Hohenberger W, Meyer T. Changes in indication and results after resection of hepatic metastases from noncolorectal primary tumors: a single-institutional review. Ann Surg Oncol 2005;12:778–785.
23. Elias D, Cavalcanti de AA, Eggenspieler P, Plaud B, Ducreux M, Spielmann M, Theodore C, Bonvalot S, Lasser P. Resection of liver metastases from a noncolorectal primary: indications and results based on 147 monocentric patients. J Am Coll Surg 1998;187: 487–493.
24. Ercolani G, Grazi GL, Ravaioli M, Ramacciato G, Cescon M, Varotti G, Del GM, Vetrone G, Pinna AD. The role of liver resections for noncolorectal, nonneuroendocrine metastases: experience with 142 observed cases. Ann Surg Oncol 2005;12:459–466.
25. Laurent C, Rullier E, Feyler A, Masson B, Saric J. Resection of noncolorectal and nonneuroendocrine liver metastases: late metastases are the only chance of cure. World J Surg 2001;25:1532–1536.
26. Takada Y, Otsuka M, Seino K, Taniguchi H, Koike N, Kawamoto T, Koda K, Adachi S, Yuzawa K, Nozue M, Todoroki T, Fukao K. Hepatic resection for metastatic tumors from noncolorectal carcinoma. Hepatogastroenterology 2001;48:83–86.
27. Weitz J, Blumgart LH, Fong Y, Jarnagin WR, D'Angelica M, Harrison LE, DeMatteo RP. Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. Ann Surg 2005;241:269–276.
28. Detry O, Warzee F, Polus M, De RA, Meurisse M, Honore P. Liver resection for noncolorectal, nonneuroendocrine metastases. Acta Chir Belg 2003;103:458–462.
29. Earle SA, Perez EA, Gutierrez JC, Sleeman D, Livingstone AS, Franceschi D, Levi JU, Robbins C, Koniaris LG. Hepatectomy enables prolonged survival in select patients with isolated noncolorectal liver metastasis. J Am Coll Surg 2006;203:436–446.
30. Zacherl J, Zacherl M, Scheuba C, Steininger R, Wenzl E, Muhlbacher F, Jakesz R, Langle F. Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. J Gastrointest Surg 2002;6:682–689.
31. Hemming AW, Sielaff TD, Gallinger S, Cattral MS, Taylor BR, Greig PD, Langer B. Hepatic resection of noncolorectal nonneuroendocrine metastases. Liver Transpl 2000;6:97–101.
32. Staehler MD, Kruse J, Haseke N, Stadler T, Roosen A, Karl A, Stief CG, Jauch KW, Bruns CJ. Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. World J Urol 2010;28:543–547.
33. Maluccio M, Einhorn LH, Goulet RJ. Surgical therapy for testicular cancer metastatic to the liver. HPB (Oxford) 2007;9:199–200.
34. Temkin SM, Fleming G. Current treatment of metastatic endometrial cancer. Cancer Control 2009;16:38–45.
35. Elias D, Lasser PH, Montrucolli D, Bonvallot S, Spielmann M. Hepatectomy for liver metastases from breast cancer. Eur J Surg Oncol 1995;21:510–513.
36. Mariani P, Servois V, De RY, Bennett SP, Feron JG, Almubarak MM, Reyal F, Baranger B, Pierga JY, Salmon RJ. Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. Eur J Surg Oncol 2013;39: 1377–1383.
37. Sakamoto Y, Sano T, Shimada K, Esaki M, Saka M, Fukagawa T, Katai H, Kosuge T, Sasako M. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. J Surg Oncol 2007;95:534–539.
38. Slotta JE, Schuld J, Distler S, Richter S, Schilling MK, Kollmar O. Hepatic resection of non-colorectal and non-neuroendocrine liver metastases—survival benefit for patients with non-gastrointestinal primary cancers—a case-controlled study. Int J Surg 2014;12:163–168.
39. Groeschl RT, Nachmany I, Steel JL, Reddy SK, Glazer ES, de Jong MC, Pawlik TM, Geller DA, Tsung A, Marsh JW, Clary BM, Curley SA, Gamblin TC. Hepatectomy for noncolorectal non-

neuroendocrine metastatic cancer: a multi-institutional analysis. J Am Coll Surg 2012;214:769–777.
40. Adam R, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, Jaeck D, Saric J, Le Treut YP, Belghiti J, Mantion G, Mentha G. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. Ann Surg 2006;244:524–535.
41. de Jong MC, Tsai S, Cameron JL, Wolfgang CL, Hirose K, van Vledder MG, Eckhauser F, Herman JM, Edil BH, Choti MA, Schulick RD, Pawlik TM. Safety and efficacy of curative intent surgery for peri-ampullary liver metastasis. J Surg Oncol 2010;102:256–263.
42. Ochiai T, Sasako M, Mizuno S, Kinoshita T, Takayama T, Kosuge T, Yamazaki S, Maruyama K. Hepatic resection for metastatic tumours from gastric cancer: analysis of prognostic factors. Br J Surg 1994;81:1175–1178.
43. Takemura N, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, Hiki N, Sano T, Yamamoto J, Kokudo N, Yamaguchi T. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. Langenbecks Arch Surg 2012;397:951–957.
44. Metcalfe MS, Mullin EJ, Maddern GJ. Hepatectomy for metastatic noncolorectal gastrointestinal, breast and testicular tumours. ANZ J Surg 2006;76:246–250.
45. DeMatteo RP, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF. Results of hepatic resection for sarcoma metastatic to liver. Ann Surg 2001;234:540–547.
46. Agarwala SS, Eggermont AM, O'Day S, Zager JS. Metastatic melanoma to the liver: a contemporary and comprehensive review of surgical, systemic, and regional therapeutic options. Cancer 2014;120:781–789.

Liver INTERNATIONAL

Liver International ISSN 1478-3223

CANCER

Time-dependent impact of age and comorbidities on long-term overall survival after liver resection

Tobias S. Schiergens[1], Andrea Lindenthaler[1], Michael N. Thomas[1], Markus Rentsch[1], Laura Mittermeier[2], Katharina Brand[2], Helmut Küchenhoff[2], Serene Lee[1], Markus Guba[1], Jens Werner[1] and Wolfgang E. Thasler[1]

1 Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Hospital of the University of Munich, Munich, Germany
2 Statistical Consulting Unit, Department of Statistics, Ludwig-Maximilians-University, Munich, Germany

Liver Int. 2016; 36: 1340–1350. DOI: 10.1111/liv.13068

Abstract

Background & Aims: Advanced age and comorbidities are known to be associated with increased perioperative risks after liver resection. However, the precise impact of these variables on long-term overall survival (OS) remains unclear. Thus, the aim of this study was to evaluate the confounder-adjusted, time-dependent effect of age and comorbidities on OS following hepatectomy for primary and secondary malignancies. *Methods:* From a prospective database of 1.143 liver resections, 763 patients treated for primary and secondary malignancies were included. For time-varying OS calculations, a Cox–Aalen model was fitted. The confounder-adjusted hazard was compared with mortality tables of the German population. *Results:* Overall, age ($P = 0.003$) and comorbidities ($P = 0.001$) were associated with shortened OS. However, time-dependent analysis indicated that age and comorbidities had no impact on OS within 39 and 55 months after resection respectively. From this time on, a significant decline in OS was shown. Subgroup analysis indicated an earlier increase of the effect of age in patients with hepatocellular carcinoma (17 months) than in those with colorectal metastases (70 months). The confounder-adjusted hazard of 70-year-old patients was increased post-operatively but dropped 66 months after surgery, and the risk of death was comparable to the general population 78 months after resection. At this time, one-third of patients aged 70 years and older were still alive. *Conclusions:* With regard to long-term outcome, liver resection for both primary and secondary malignancies should not be categorically denied due to age and comorbidities. This information should be considered for the patient selection process and informed consent.

Keywords

age – comorbidities – Cox–Aalen model – liver resection – time-varying coefficients

Ageing of the Western population and advances in perioperative care and surgical techniques have resulted in an increase in the number of elderly patients being scheduled for resection of primary and secondary liver tumours (1–4). In Europe, life expectancy at the age of 65 is projected to increase by 5.4 years for men and 5.2 years for women, ultimately reaching 21.8 and 25.1 years by 2060 respectively (5). Based on the ageing of the 'baby boomer generation' (patients born from 1945 to 1965) (6), cancer-related death is expected to increase dramatically, especially in the elderly population. Despite medical improvements, advanced age and underlying illness are known to be crucial risk factors for increased morbidity and mortality after major abdominal surgery (i.e. liver resection), mostly due to extensive comorbidities, decreased physiologic reserve and malnutrition (4, 7–10). The decision as to whether a patient should undergo hepatic resection,

Abbreviations

AIC, Akaike information criterion; ASA, American Association of Anesthesiologists; CCI, Charlson comorbidity index; CD, Clavien–Dindo classification; CLM, colorectal liver metastasis; CRF, case report form; HCC, hepatocellular carcinoma; HLOS, hospital length of stay; ICU, intensive care unit; NCRNNE, non-colorectal non-neuroendocrine liver metastasis; OS, overall survival; UICC, Union Internationale Contre le Cancer.

Correspondence

Wolfgang E. Thasler, Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Hospital of the University of Munich, Marchioninistr. 15, D-81377 Munich, Germany
Tel: +49 89 4400 73560 Fax: +49 89 4400 75464
e-mail: wolfgang.thasler@med.lmu.de

Handling Editor: Gabriele Missale

Received 1 September 2015; Accepted 7 January 2016

Key points

- The precise impact of age and comorbidities on long-term survival after liver surgery remains unclear.
- Applying a novel statistical method – the Cox–Aalen-model – we are able to report the time-dependent impact of these variables on long-term outcome after hepatectomy.
- We observe that age has no impact on survival within the first 39 months after operation. Additionally, comorbidities do not decrease survival within the first 5 years.
- Regarding long-term outcome, liver resection for both primary and secondary malignancies should not be categorically denied due to age and comorbidities.

however, is not only influenced by considerations regarding periprocedural risks but also by the expected long-term survival. In this context, life expectancy of older and especially comorbid patients is often underestimated by healthcare professionals (11), which, in some cases, may lead to the denial of surgical treatment.

Several studies have assessed the impact of age and comorbidities on outcome after liver resection (4, 8, 10, 12–25), although most have focused on early post-operative outcome. It is clear that patient age and severe comorbidities are statistically relevant prognostic factors when long-term survival is assessed, as these variables considerably shortened life span regardless of surgery (4, 8). Within the limits of standard regression models (i.e. Cox's model) which need to hold the proportionality assumption (26, 27), statistical calculations only provide rough summaries of the impact of age and comorbidities and thus are unable to give precise information of the variables' temporal evolvement after surgery. Due to this missing information and potential regression model misspecification, there is a continuing controversy on the exact role of age and comorbidities in this patient population. Thus, improved and more detailed knowledge is important for a better understanding of the role of these key variables. This necessitates the application of extended and more complex regression models to specify the time-varying impact of these variables on long-term survival. This is enabled by the new flexible additive-multiplicative regression method of the Cox–Aalen survival model (28, 29). Aalen *et al.* proposed an additive hazard model which allowed the coefficients to be a function of time and that the effect of a covariate may vary over time (30). Like an additive Aalen model, the Cox–Aalen model consists of two parts, an additive (Aalen) component and a multiplicative (Cox regression) component. Thus, this model was chosen in the present analysis to gain a more detailed understanding of the relationship between age as well as comorbid conditions and long-term outcomes of patients undergoing liver resection. This may help surgeons improve patient selection and informed consent.

The aim of this study was to assess the confounder-adjusted and time-dependent effect of age and comorbidities on the overall survival (OS) of post-acute survivors after liver resection for primary and secondary hepatic malignancies in a high-volume single centre and to compare the multivariate-adjusted, time-dependent hazard of elderly patients to that of the general population.

Patients and methods

Design and study population

The data from patients undergoing elective, curative-intended liver resection for primary or secondary hepatic malignancies between 2003 and 2013 were prospectively collected. Patients who died within 90 post-operative days were excluded from outcome analysis because the effect of age and comorbidities on long-term survival of post-acute survivors was of specific interest. This enabled survival analysis independently of biasing mortality effects caused by age and comorbidities as these have been identified as risk factors for increased perioperative mortality in several studies (6, 7, 10, 31). This was confirmed for the present population in a recent analysis, too (32). This study was approved by the Ethics Committee of the Faculty of Medicine, Ludwig-Maximilians-University. Design, data acquisition, statistical methods and manuscript preparation were carried out according to the STROBE guidelines for the strengthening of observational studies (33).

Data assessment

For prospective, standardised data assessment, electronic case report forms (CRF) were used as previously reported (4). Comorbidities were stratified by applying the classifications of the American Association of Anesthesiologists (ASA) and the Charlson comorbidity index (CCI) (34). Tumour stages were classified according to UICC and the Bismuth–Corlette classification for Klatskin tumours (35, 36). Major liver resection was defined as hemi-hepatectomy or extended hemi-hepatectomy. Post-operative morbidity was assessed according to the validated Clavien–Dindo classification (CD) (37). OS was determined from the date of liver resection to the date of death or last recall.

Statistical analysis

For statistical analysis, the R-language [version 3.0.2, packages (38–42)] and SPSS (version 22.0; IBM, Chicago, IL, USA) were used. $P < 0.05$ was considered statistically significant. Results were expressed as numbers and percentages for binomial variables and as median and range [minimum and maximum] for continuous variables. Univariate survival analysis was performed by Kaplan–

Meier plots describing 5-year survival and by applying the log-rank test for statistical discrimination of binominal variables. The log-rank test was limited to 5-year survival because of censored patients. The numbers of patients at risk were added to the Kaplan–Meier survival estimator. For continuous variables, a Cox regression model was calculated. For estimation of multivariate, confounder-adjusted time-varying effects, the Cox–Aalen survival model (29) based on splines was applied. Therefore, all variables were systematically selected by the Akaike information criterion (AIC) (43), thereby including the best fitting confounder variable effect. This forward inclusion procedure also leads to the exclusion of univariately significant associated variables. For comparison of confounder-adjusted hazards derived from the Cox–Aalen model with primary tumours as statistical reference with those of the general population, mortality tables of the German Federal Statistical Office, Wiesbaden (2009–2011), which considered the age- and gender-specific mortality rates of the German population, were applied (44). Hazard rates were evaluated on the basis of 12-month intervals. To consider the bias caused by involvement of different tumour entities, an additional Cox–Aalen model was fitted including the prognostic coefficients of different tumour types. After elimination of the covariable metastatic disease, the tumour entities were entered into the model parameterised as colorectal liver metastases (CLM), non-colorectal liver metastases, hepatocellular carcinoma (HCC) and cholangiocarcinoma, Klatskin tumours as well as gallbladder carcinomas, whereas CLM was set as statistical reference. Additionally, for the largest subpopulations of CLM, non-colorectal non-neuroendocrine metastases (NCRNNE), and HCC subgroup, analyses were performed creating a separate Cox–Aalen model.

Results

Patient population

Between 2003 and 2013, 1.143 liver resections were performed at our institution. Of those, 1032 patients underwent resection for primary and secondary malignancies. After exclusion of 269 patients due to incomplete CRF and incomplete follow-up, 763 cases were assessed for this study. Subsequently, 55 patients who died within 90 post-operative days (7%, 90-day mortality) were excluded, and post-acute survivors ($N = 708$) were defined as the study population for analysis of long-term survival. Within 30 post-operative days, 32 patients (4%, 30-day mortality) died.

Clinical characteristics and univariate survival analysis

Baseline characteristics, clinical variables associated with their 5-year survival rate and univariate survival analysis are presented in Table 1. The Kaplan–Meier plot of the study population with its 95% confidence interval (95% CI) is displayed in Fig. 1. Three hundred and twenty-two patients (46%) died by the end of the study. The median survival time was 55 months, with 5- and 10-year survival rates of 46% and 31% respectively. The median age was 64 [18–90] years. Overall, 440 patients (62%) had secondary malignancies, while 268 (38%) had primary liver tumours, and 5-year survival rates for these groups were 47.3 and 45.3 months respectively. Among HCC patients, 46% underwent surgery at UICC stage I, 22% at stage II and 32% at stages III and IV. Forty-four per cent of patients with cholangiocarcinoma were at stage I, 24% at stage II and 32% at stage III. The Bismuth–Corlette classification revealed that 4% of patients with Klatskin tumours had type I, 14% type II, 29% type IIIA, 39% type IIIB and 14% type IV. Finally, 41% of patients with gallbladder carcinoma were at UICC stage ≥III.

Within the univariate survival analysis, there was no difference between primary tumours and liver metastases ($P = 0.978$). HCC and CLM were the most common diagnoses. Almost half of the study population (41%) had received chemotherapy. The CCI ($P = 0.001$) and the ASA score ($P = 0.022$) were significantly associated with shortened OS, which did not apply to underlying hepatic parenchymal diseases (steatosis, fibrosis, cirrhosis). Among intraoperative factors, allogeneic transfusion ($P = 0.032$), resected liver volume ($P = 0.046$) and the number of liver tumours ($P = 0.016$) were identified as prognostic factors. Three hundred and three patients (43%) developed post-operative complications, and 174 (25%) showed severe morbidity (CD > II). The incidence of complications ($P = 0.026$), severe ($P = 0.010$) and non-surgical morbidity ($P = 0.005$) was associated with decreased OS.

Multivariate survival analysis with time-dependent effects

As a continuous variable, age at resection was associated with reduced survival when univariate analysis was performed ($P = 0.003$; Table 1). The final Cox–Aalen survival model revealed that age, comorbidities and whether the underlying disease was a primary or secondary malignancy were time-varying variables. To adjust for confounding prognostic covariables, (female) gender ($P = 0.016$; HR, 1.32; 95% CI, 1.05–1.67), major liver resection ($P = 0.122$; HR, 1.20; 95% CI, 0.94–1.53), perioperative transfusion ($P = 0.131$; HR, 1.21; 95% CI, 0.95–1.53) and severe post-operative complications ($P = 0.140$; HR, 1.21; 95% CI, 0.94–1.56) were included as time-constant proportional terms. The time-varying effects for age and CCI are plotted in Fig. 2. The lower 95% confidence band crossed the horizontal axis (coefficient = 0) at 39, 55 and 60 months for age, CCI and metastatic disease respectively. From this time on, a significant independent reduction in survival by the respective variable was assumed. Of note, the coefficient's unit of patient age was lower (approximately 10-fold) than that of CCI and metastasis (Fig. 2). The additional Cox–Aalen model including the propor-

Table 1. Clinical characteristics and univariate survival analysis

	No. of patients *N* (%)	5-year survival %	*P*
Age at resection	64.0 [18–90]*	n./a.	0.003
Gender			
Female	291 (45)	50.2	0.142
Male	417 (55)	40.6	
Diagnosis			
Primary malignancy	268 (38)	45.3	0.978
Metastases	440 (62)	47.2	
Primary malignancies			
Hepatocellular carcinoma†	150 (21)	47.7	
Cholangiocarcinoma‡	69 (10)	39.6	
Klatskin tumour§	31 (4)	50.4	
Gallbladder carcinoma¶	18 (3)	34.2	
Metastases			
Colorectal, synchronous**	97 (14)	51.5	
Colorectal, metachronous	175 (25)	45.5	
Neuroendocrine	20 (3)	75.4	
Non-colorectal, non-neuroendocrine	148 (21)	36.4	
Comorbidities			
ASA			
>2	455 (64)	42.2	0.022
≤2	253 (36)	52.1	
CCI††			
>2	296 (42)	39.8	0.001
≤2	412 (58)	51.6	
Previous chemotherapy	286 (41)	43.3	0.227
Liver disease			
Steatosis	341 (48)	45.4	0.406
Fibrosis	162 (23)	44.8	0.186
Cirrhosis	67 (9)	43.8	0.998
Extent of resection			
Major hepatectomy	223 (32)	40.3	0.318
Minor hepatectomy	485 (68)	48.6	
Ischaemic manoeuvre	159 (22)	49.5	0.279
Estimated blood loss			
≥500 ml	401 (57)	45.4	0.289
<500 ml	307 (43)	47.4	
Perioperative transfusion	245 (35)	37.8	0.032
Resected liver volume			
≥200 ml	375	40.9	0.046
<200 ml	333	52.1	
Maximum tumour diameter			
≥50 mm	199 (28)	42.0	0.396
<50 mm	509 (72)	53.4	
No. of liver tumours			
≥3	98 (14)	30.2	0.016
2	95 (13)	50.1	
1	515 (73)	47.1	
Margins involved (R1)	59 (8)	34.1	0.119
Total complications	303 (43)	40.9	0.026
Severe complications‡‡	174 (25)	39.2	0.010
Surgical complications			
Secondary haemorrhage	18 (3)	33.3	0.071
Abscess	29 (4)	31.1	
Bile leak/biloma	53 (7)	26.4	
Wound infection	50 (7)	37.5	
Paralytic ileus	44 (6)	39.7	
Non-surgical complications			
Acute coronary syndrome	25 (4)	28.6	0.005
Respiratory failure	47 (7)	25.3	
Pneumonia	23 (3)	30.4	
Liver dysfunction/failure	28 (4)	38.4	
Total HLOS§§			
≥12 days	363 (51)	40.7	<0.001
<12 days	345 (49)	51.4	
ICU LOS			
≥2 days	168 (24)	42.2	<0.001
1–2 days	227 (32)	41.2	

*Numbers as median and [range].
†UICC stages: I, 46%; II, 22%; III and IV, 32%.
‡UICC stages: I, 44%; II, 24%; III, 32%.
§Bismuth–Corlette classification: type I, 4%; type II, 14%; type IIIA, 29%; type IIIB, 39%; type IV, 14%.
¶Forty-one per cent were at UICC stage ≥III.
**Assessed before or within 3 months after primary tumour resection.
††Charlson comorbidity index.
‡‡Clavien–Dindo >II.
§§Hospital length of stay.

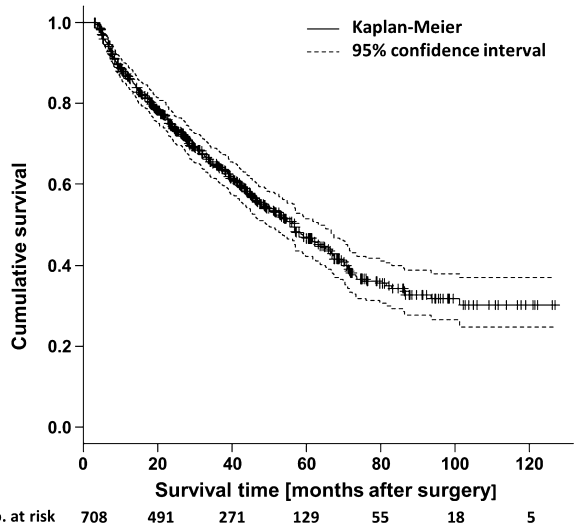


Fig. 1. Kaplan–Meier estimate of the study population with its 95% confidence interval (*N* = 708). The median survival was 55 months with 5- and 10-year survival rates of 46% and 31% respectively.

tional time-constant effects of different tumour entities revealed that the time-dependent effects of age and comorbidities were qualitatively and quantitatively comparable to the final model. In that additional model, the coefficients of age and CCI became significant at 37 and 54 months after surgery respectively.

Figure 3 shows the confounder-adjusted survival plots of the final Cox–Aalen model stratified by patient

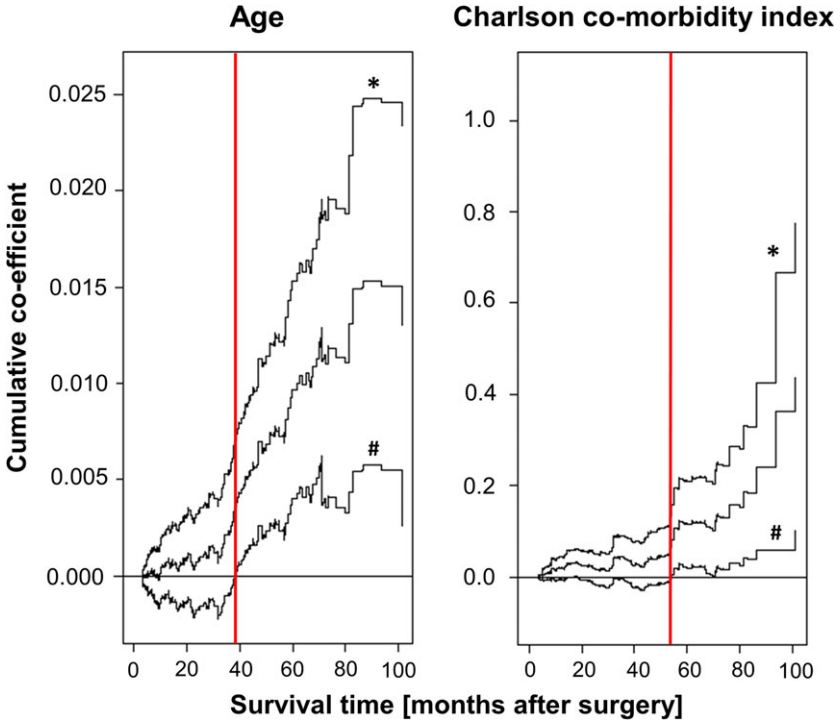


Fig. 2. Final Cox–Aalen survival model displaying the time-dependent effects (cumulative coefficients) of age and comorbidities adjusted for prognostic confounders such as gender, major liver resection, perioperative transfusion and severe post-operative complications (cumulative risk estimator, upper (*) and lower (#) 95% confidence bands). The lower 95% confidence band crosses the horizontal axis (coefficient = 0, red line) at 37 months for age and at 54 months for the Charlson comorbidity index. From this time on, a significant independent reduction in survival by the respective variable is assumed. In contrast to age, the coefficient's incline of comorbidities was more linear and more restrained.

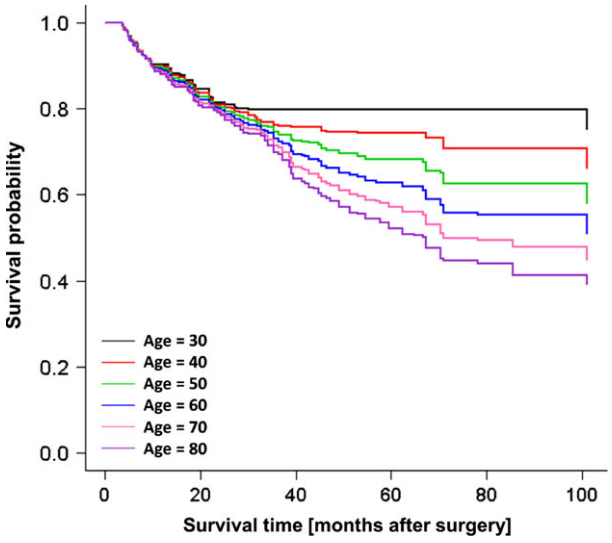


Fig. 3. Confounder-adjusted survivor plots (Cox–Aalen model) stratified by patient age per decade. The curves run very close together within the post-operative period. Between 30 and 40 months post operation, they progressively spread apart, indicating a relevant and increasing impact of age on long-term survival.

age per decade. The curves run very close together within the first years after hepatectomy; however, between 30 and 40 months post operation, the curves progressively spread apart indicating a relevant and increasing impact of age on long-term survival.

Compared with the German population (Fig. 4), the confounder-adjusted hazards of both female and male post-acute survivors at age 70 increased post-operatively. The initial differences between the patients' and the German population's hazard were more distinct in women than in men, as the hazard rates of female patients were higher and those of the female population were lower compared with men. Sixty-six months after surgery, the hazard rates started dropping and relevantly decreased. They became comparable with the mortality table at approximately 78 months after resection. Thirty-six per cent of female and 31% of male patients aged 70 years and older of the entire population were still alive at this point after resection.

Subgroup analysis with time-dependent effects

The time-dependent effects of age and CCI of the largest subpopulations CLM, HCC and NCRNNE are displayed in Fig. 5. For CLM (Fig. 5A), there was a

Liver International (2016)

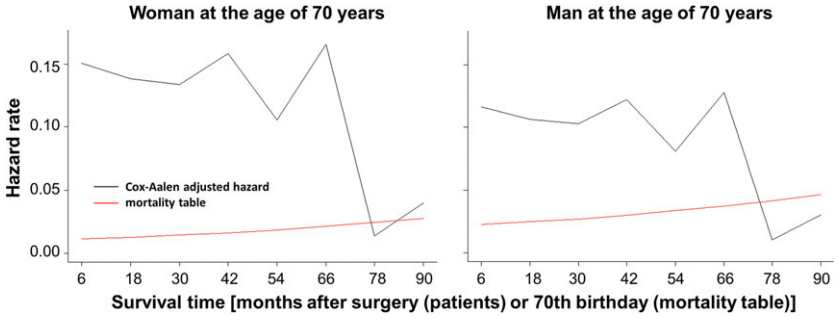


Fig. 4. Confounder-adjusted hazard rates with primary tumours set as statistical reference for both female and male post-acute survivors at age 70 compared to the hazard rate of the German population. Sixty-six months after surgery, the hazard began to drop and became comparable with the mortality table at approximately 78 months after resection. This corresponds to the statistical cure of the patients' disease. Approximately one-third of patients aged 70 years and older were still alive at this time.

low but constant increase for age; the abscissa was crossed by the lower confidence band at 70 months after surgery. Initially, no effect was seen for comorbidities; however, a relevant but insignificant increase was observed at 43 months. Among HCC patients (Fig. 5B), age became significant at 17 months. For comorbidities, the effect was not significant, however, with an increase at 54 months. In NCRNNE patients, a constant but insignificant increase of the coefficient of age was shown at 23 months with no relevant impact of comorbidities until 42 months after surgery (Fig. 5C).

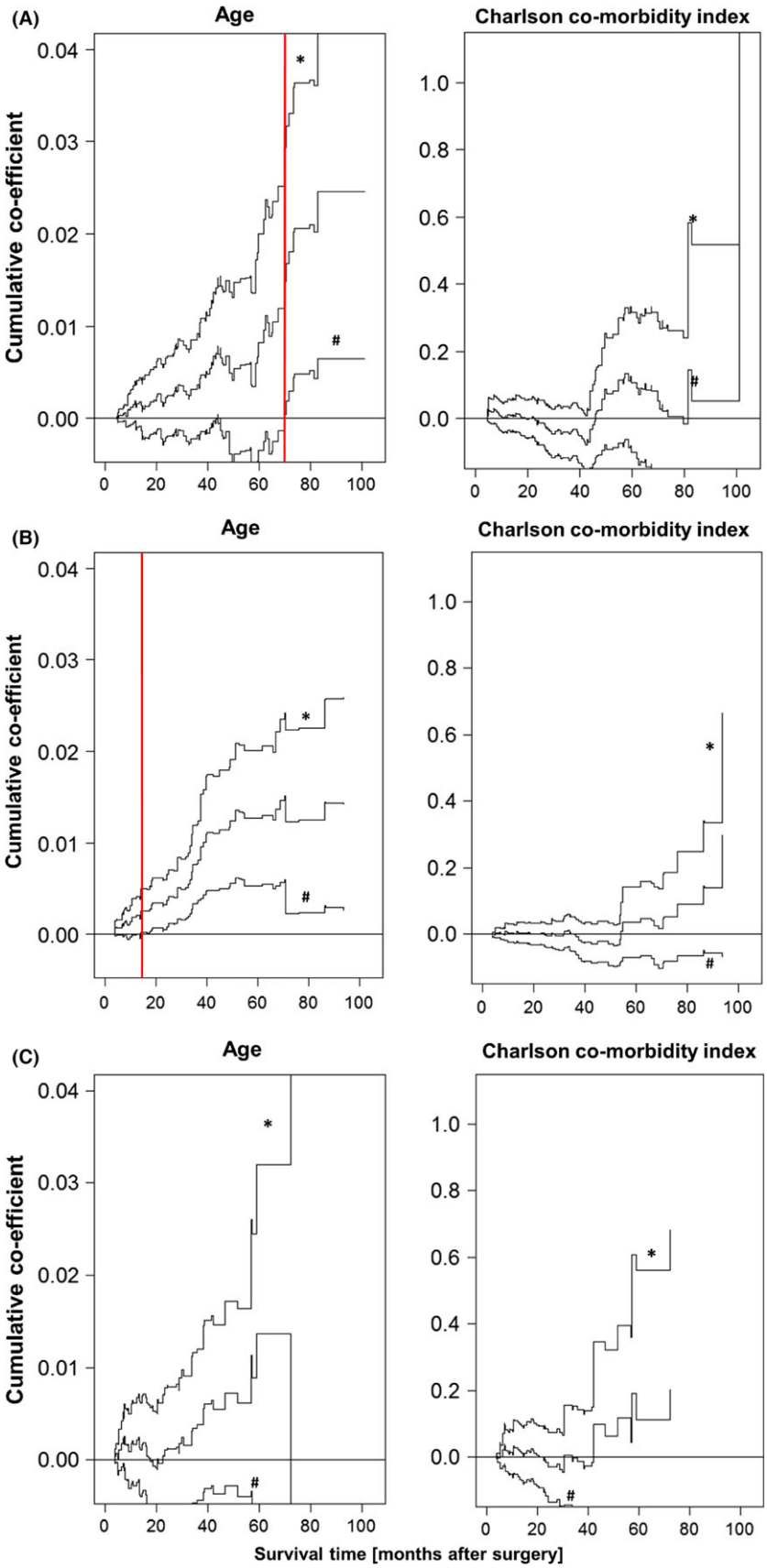
Discussion

This study suggests that patient age has no impact on long-term survival in post-acute patients within the first 3 years after liver resection. Even after this phase, the effect stays low when adjusted for confounders such as comorbid illnesses. Additionally, comorbidities do not decrease survival relevantly within the first 5 years after surgery. These results are corroborated after adjustment for the prognostic effects of different tumour types involved in this study. Subgroup analysis reveals that the effect of age becomes significant at 70 months after surgery for CLM patients and at 17 months for HCC patients. Sixty-six months after resection, the confounder-adjusted mortality risk of a 70-year-old patient relevantly drops and reaches the level of the general population by 78 months. This time point is reached by at least one-third of the septuagenarians of the entire population, indicating that elderly long-term survivors seem to have a prognosis similar to the general population after 6.5 years.

Following liver resection and other major abdominal surgery, the effect of age and comorbidities on morbidity and post-operative mortality has been extensively assessed with partially conflicting results (2, 8, 10, 12, 14, 20, 21, 23, 45–48). These discrepancies may be explained by differences in the population risk profiles, patient selection and aggressiveness of resection. Results from larger observational studies indicate a substantially higher perioperative risk for patients of advanced age (6, 7, 10, 31), as the stress of major surgery may not be well tolerated due to decreased physiologic reserves and the concomitance of medical disease. Additionally, frailty of the elderly is an often underestimated problem for increased perioperative risk (6). To decrease post-operative morbidity and mortality, selection of elderly patients scheduled for hepatectomy should essentially concern the disease and the adequate extent and quality of surgery as well as perioperative care rather than chronological age (4).

A conservative approach to patient selection may be explained by the expectation of higher morbidity and mortality as well as the anticipation of a shorter life span. The remaining life time, however, is not only underestimated in the comorbid elderly (11) but also plays a decisive role in the surgeon's considerations regarding the indication for liver resection. In turn, overcautious attitudes towards surgery carry the danger of unjustified denial of tumour resection. Hence, a precise and confounder-adjusted description of the impact of age and comorbidities on independent long-term

Fig. 5. Subgroup analysis with time-dependent effects of age and comorbidities of the largest subpopulations colorectal liver metastases (CLM), hepatocellular carcinoma (HCC) and non-colorectal non-neuroendocrine metastases (NCRNNE). For CLM (A), the horizontal axis (coefficient = 0, red line) was crossed by the lower confidence band (#) at 70 months after surgery. Initially, no effect was seen for comorbidities; however, a relevant but insignificant increase was observed at 43 months. For HCC patients (B), age became significant earlier at 17 months (red line). Regarding comorbidities, the effect was not significant, however, with an increase at 54 months. In the NCRNNE subgroup (C), a constant but insignificant increase of the coefficient of age was shown at 23 months with no relevant impact of comorbidities until 42 months after surgery.



Liver International (2016)

outcomes is of major interest for reasonable patient selection and informed consent. It is in the very nature of things that age and comorbidities are statistically associated with declined survival (4, 8). Descriptions of this association are commonly impaired by the higher risk of all-cause mortality in elderly patients who are more frequently affected by comorbid illnesses (6, 12, 18, 19). Statistically, this correlation is commonly calculated by roughly summarising standard regression models which are applied because they are intuitive and simple to fit and the results are easy to explain (49). However, these models do assume that each explanatory variable's effect remains constant over time, thereby relying on the proportional hazards assumption. However, this assumption cannot be accepted as true for patient age and underlying illness. A calculation of time-dependent effects is enabled by extended regression models such as the Cox–Aalen model (29). This very flexible model combines a multiplicative and an additive component, thereby allowing some covariate effects to be additive, non-parametric and time-varying (29). With regard to the selection of covariables, Cox's and Cox–Aalen models are comparable (49). When adjusted for prognostic confounders such as gender, extent of hepatic resection, need for perioperative transfusion and post-operative complications (4, 8, 20, 50), we were able to describe the time-dependent impact of patient age and medical comorbidities. These calculations are closer to reality than hazard rates calculated based on individual age cut-offs within standard models and give a more comprehensive understanding of the data. Moreover, the Cox–Aalen model specifically enabled to describe the confounder-adjusted survival of 70-year-old patients as well as the confounder-adjusted comparison to the mortality tables of the general population.

Comorbidities are routinely categorised using the well-established CCI (34). In our population, comorbidities were identified as an independent risk factor for post-operative mortality (data not shown) and shortened OS within univariate analysis. These results corroborate previous findings on the clear association between medical illness and survival (8). On the one hand, this fact underlines the vital importance of considering comorbidities for patient selection regarding periprocedural risks, whereas on the other hand, this highlights the importance of describing the time-dependent effect on long-term outcome independently of deaths occurring within the acute post-operative phase.

For a period of 39 months after resection, there was no decrease in survival by age. Thereafter, the impact of chronological age continuously increased. The extent of this association indicated by the cumulative coefficient was far lower than that of comorbid illnesses. This result shows that the effect of chronological age is diminished or rescinded when comorbidities are adjusted. This observation is confirmed by the additional Cox–Aalen model after adjustment for different tumour types and by the subgroup analyses for CLM, HCC and NCRNNE. Thus, not only for patient selection but also in view of long-term survival, our results indicate that liver resection in the elderly should focus on disease rather than age. Taking 5-year survival rates into account (Table 1) and given that 39 months post resection were reached by 62% of patients with HCC, 56% of those with cholangiocellular carcinoma, 66% of patients with CLM and even by 54% of patients with NCRNNE, our results demonstrate that mainly periprocedural risks should be considered for liver resection in these patients.

On subgroup analysis, the coefficient of age rose earlier in HCC patients and became significant at 17 months. In this subpopulation, 81% of HCC patients were alive at that time. However, at approximately 40 months, a plateau was reached (Fig. 5B). Admittedly, it seems that there is an earlier effect of age on survival than in patients with liver metastases; however, the effect was overall low. These results may be partially explained by the higher severity of underlying diseases in HCC patients (i.e. complications occurring in the further course of the disease caused by the underlying liver disease) despite statistical adjustment to the preoperative CCI. This indicates that a very careful patient selection is necessary. In the light of the long-term outcome of HCC patients and regarding the fact that surgery and transplantation are the best treatment strategies concerning overall survival, our results indicate that physicians and surgeons should adapt patient selection for surgery to perioperative risk factors and extent of cancer regardless of the patients' age. This is supported by another study with survival rates in patients undergoing surgery that are comparable to ours (47). Propensity analysis in this study revealed that advanced age had no impact on the outcome of patients undergoing liver resection (47).

The more aggressive approach towards surgery in patients with liver metastases, which is increasingly being adopted in tertiary centres within multimodal treatment strategies, seems to be justified by our data: Within the first 5 years after surgery, there were no differences in long-term survival between patients with resection of primary and secondary liver tumours. For CLM patients, the subgroup analysis showed a low but constant increase for age with significant increase at 70 months after surgery. In the NCRNNE subgroup, a constant but insignificant increase of the coefficient of age was shown at 23 months. These findings corroborate the established benefit of surgery for CLM (58-month median survival) (51–54) and also confirm the utility of resection for NCRNNE (35-month median survival) (4). In the light of the excellent outcomes of CLM patients undergoing surgery and the risk factors that were identified, Adam *et al.* also concluded that there should be no upper age limit when patient selection is adequately done (55).

When a 70-year-old patient was considered, the risk of death was comparable to that of the general population six and a half years after the operation when adjusted for confounding variables with primary tumours as statistical reference. This corresponds to the statistical cure of the patients' disease, and approximately one-third of patients aged 70 years and older were alive at this time. These results, however, could not be affirmed in the additional Cox–Aalen model; this seems to be attributed to the change in the coefficients with elimination of the time-varying variable 'metastasis' and the addition of several coefficients of different tumour types which seems to have resulted in an overparameterisation of this additional model especially when this late time phase after surgery is considered. Furthermore, when secondary tumours were set as statistical reference, the mortality risk also massively dropped but only almost reached the level of the general population at 78 months. In addition, the comparison between patients undergoing surgery and the general population may be biased by preselection of patients regarding operability which might have also included concerns about age and comorbid conditions. However, these interesting results highlight our conclusion that liver surgery for the elderly should not be denied in general based on chronological age and comorbidities.

Not only due to medical and social but also economic considerations, hepatic resections have come under increasing scrutiny because they are among the most expensive abdominal surgical procedures (3). Even when considering the enormous cost pressure, our data suggest that hepatic resection is justified in the elderly just as in younger counterparts with the prospect of long-term outcome. In this context, Vickers *et al.* were able to demonstrate that perioperative costs for major abdominal surgery were comparable between patients ≥70 years and those <70 years. Thus, despite extensive pressure to control costs, longevity among old patients demonstrated by this study, even among those with liver metastases, calls economic limitations into question.

Our analysis is subject to some limitations. First, our findings may not be entirely generalisable as they represent the experience with a single-centre population and thereby reflect a unique case mix. The validity of our findings, however, is affirmed by prospective and standardised assessment of demographic, medical, oncological and perioperative data from surgical and perioperative high-quality treatments (56) in a tertiary referral cancer centre. Furthermore, our results were not subject to significant secular trends and a sufficient long-term follow-up was obtained. Despite the recognised validity of the CCI, which was used to classify comorbidities in our cohort, the interindividual range of comorbidities must be considered in order to make careful decisions especially regarding major surgery. Additionally, different tumour types with different adjuvant treatment options, efficacy and prognosis were included in this study. To address this bias, the additional Cox–Aalen model was fitted including the prognostic coefficients of different tumour entities. However, this additional model bears the risk to be overparameterised. In this context of lower statistical power, the subgroup analyses also have to be interpreted with caution. No statistically reliable Cox–Aalen model could be fitted for the small subgroups included in this study. Finally, besides perioperative considerations, the prospect of long-term benefit dependent on the individual oncological situation has to be carefully assessed.

Conclusion

In case of liver resection of primary and secondary malignancies, the stringency of patient selection based on age and comorbidities should be essentially referred to periprocedural risks, as age and comorbidities were observed to show no impact on long-term survival within 4 years after surgery. Our results, therefore, suggest that liver surgery even for metastatic disease should be offered to elderly patients whenever they are fit enough for the surgical procedure.

Acknowledgements

The authors thank Dr Hans-Martin Hornung and Mrs Gabriele Kramer for their dedicated IT administration of the liver database.

Financial support: No funding was received for this study.

Conflict of interest: The authors do not have any disclosures to report.

References

1. Belghiti J, Hiramatsu K, Benoist S, *et al.* Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 2000; **191**: 38–46.
2. Ijtsma AJ, Boeve LM, van der Hilst CS, *et al.* The survival paradox of elderly patients after major liver resections. *J Gastrointest Surg* 2008; **12**: 2196–203.
3. Petrowsky H, Clavien PA. Should we deny surgery for malignant hepato-pancreatico-biliary tumors to elderly patients? *World J Surg* 2005; **29**: 1093–100.
4. Schiergens TS, Stielow C, Schreiber S, *et al.* Liver resection in the elderly: significance of comorbidities and blood loss. *J Gastrointest Surg* 2014; **18**: 1161–70.
5. The 2009 Ageing Report. *Underlying Assumptions and Projection Methodologies*. Brussels, Belgium: European Commission, 2009.
6. Al-Refaie WB, Parsons HM, Henderson WG, *et al.* Major cancer surgery in the elderly: results from the American College of Surgeons national surgical quality improvement program. *Ann Surg* 2010; **251**: 311–8.
7. Massarweh NN, Legner VJ, Symons RG, McCormick WC, Flum DR. Impact of advancing age on abdominal surgical outcomes. *Arch Surg* 2009; **144**: 1108–14.

8. Menon KV, Al-Mukhtar A, Aldouri A, *et al.* Outcomes after major hepatectomy in elderly patients. *J Am Coll Surg* 2006; **203**: 677–83.
9. Pasetto LM, Lise M, Monfardini S. Preoperative assessment of elderly cancer patients. *Crit Rev Oncol Hematol* 2007; **64**: 10–8.
10. Reddy SK, Barbas AS, Turley RS, *et al.* Major liver resection in elderly patients: a multi-institutional analysis. *J Am Coll Surg* 2011; **212**: 787–95.
11. Wirth R, Sieber CC. Health care professionals underestimate the mean life expectancy of older people. *Gerontology* 2012; **58**: 56–9.
12. Aldrighetti L, Arru M, Caterini R, *et al.* Impact of advanced age on the outcome of liver resection. *World J Surg* 2003; **27**: 1149–54.
13. Cescon M, Grazi GL, Del GM, *et al.* Outcome of right hepatectomies in patients older than 70 years. *Arch Surg* 2003; **138**: 547–52.
14. Ettorre GM, Sommacale D, Farges O, *et al.* Postoperative liver function after elective right hepatectomy in elderly patients. *Br J Surg* 2001; **88**: 73–6.
15. Ezaki T, Yukaya H, Ogawa Y. Evaluation of hepatic resection for hepatocellular carcinoma in the elderly. *Br J Surg* 1987; **74**: 471–3.
16. Fong Y, Brennan MF, Cohen AM, *et al.* Liver resection in the elderly. *Br J Surg* 1997; **84**: 1386–90.
17. Fortner JG, Lincer RM. Hepatic resection in the elderly. *Ann Surg* 1990; **211**: 141–5.
18. Hanazaki K, Kajikawa S, Shimozawa N, *et al.* Hepatic resection for hepatocellular carcinoma in the elderly. *J Am Coll Surg* 2001; **192**: 38–46.
19. Koperna T, Kisser M, Schulz F. Hepatic resection in the elderly. *World J Surg* 1998; **22**: 406–12.
20. Lee CR, Lim JH, Kim SH, *et al.* A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients. *J Gastrointest Surg* 2012; **16**: 1736–43.
21. Melloul E, Halkic N, Raptis DA, Tempia A, Demartines N. Right hepatectomy in patients over 70 years of age: an analysis of liver function and outcome. *World J Surg* 2012; **36**: 2161–70.
22. Mentha G, Huber O, Robert J, *et al.* Elective hepatic resection in the elderly. *Br J Surg* 1992; **79**: 557–9.
23. Shirabe K, Kajiyama K, Harimoto N, *et al.* Early outcome following hepatic resection in patients older than 80 years of age. *World J Surg* 2009; **33**: 1927–32.
24. Takenaka K, Shimada M, Higashi H, *et al.* Liver resection for hepatocellular carcinoma in the elderly. *Arch Surg* 1994; **129**: 846–50.
25. Wu CC, Chen JT, Ho WL, *et al.* Liver resection for hepatocellular carcinoma in octogenarians. *Surgery* 1999; **125**: 332–8.
26. Prentice RL, Kalbfleisch JD, Peterson AV Jr, *et al.* The analysis of failure times in the presence of competing risks. *Biometrics* 1978; **34**: 541–54.
27. Latouche A, Boisson V, Chevret S, Porcher R. Misspecified regression model for the subdistribution hazard of a competing risk. *Stat Med* 2007; **26**: 965–74.
28. Scheike TH, Zhang MJ. An additive-multiplicative Cox-Aalen regression model. *Scand J Stat* 2002; **29**: 75–88.
29. Scheike TH, Zhang MJ. Extensions and applications of the Cox-Aalen survival model. *Biometrics* 2003; **59**: 1036–45.
30. Aalen OO. A linear regression model for the analysis of life times. *Stat Med* 1989; **8**: 907–25.
31. Finlayson EV, Birkmeyer JD. Operative mortality with elective surgery in older adults. *Eff Clin Pract* 2001; **4**: 172–7.
32. Schiergens TS, Dorsch M, Mittermeier L, *et al.* Thirty-day mortality leads to underestimation of postoperative death after liver resection: a novel method to define the acute postoperative period. *Surgery* 2015; **158**: 1530–7.
33. von Elm E, Altman DG, Egger M, *et al.* The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7.
34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373–83.
35. *TNM Classification of Malignant Tumours*, 7th edn. Hoboken: Wiley-Blackwell, 2009.
36. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg* 1992; **215**: 31–8.
37. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13.
38. Harrell Frank E Jr, Dupont C. Hmisc: Harrell Miscellaneous. R package version 3.14-5. http://CRAN.R-project.org/package=Hmisc, 2014.
39. Therneau T. A Package for Survival Analysis in S. R package version 2.37-7. http://CRAN.R-project.org/package=survival>, 2014.
40. Venables WN, Ripley BD. *Modern Applied Statistics with S*, 4th edn. New York: Springer, 2002 ISBN 0-387-95457-0.
41. Scheike TH, Martinussen T. *Dynamic Regression Models for Survival Data*. New York: Springer, 2006.
42. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *J R Stat Soc B* 2011; **73**: 3–36.
43. Wagenmakers EJ, Farrell S. AIC model selection using Akaike weights. *Psychon Bull Rev* 2004; **11**: 192–6.
44. German Federal Statistical Office. Wiesbaden. Mortality Tables 2009/2011, 2014.
45. Hyder O, Pulitano C, Firoozmand A, *et al.* A risk model to predict 90-day mortality among patients undergoing hepatic resection. *J Am Coll Surg* 2013; **216**: 1049–56.
46. Kulik U, Framke T, Grosshennig A, *et al.* Liver resection of colorectal liver metastases in elderly patients. *World J Surg* 2011; **35**: 2063–72.
47. Mirici-Cappa F, Gramenzi A, Santi V, *et al.* Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-year multicentre experience. *Gut* 2010; **59**: 387–96.
48. Motoyama H, Kobayashi A, Yokoyama T, *et al.* Impact of advanced age on the short- and long-term outcomes in patients undergoing hepatectomy for hepatocellular carcinoma: a single-center analysis over a 20-year period. *Am J Surg* 2015; **209**: 733–41.
49. Abadi A, Saadat S, Yavari P, Bajdik C, Jalili P. Comparison of Aalen's additive and Cox proportional hazards models for breast cancer survival: analysis of population- based

data from British Columbia, Canada. *Asian Pac J Cancer Prev* 2011; **12**: 3113–6.
50. Mavros MN, de Jong M, Dogeas E, Hyder O, Pawlik TM. Impact of complications on long-term survival after resection of colorectal liver metastases. *Br J Surg* 2013; **100**: 711–8.
51. Brown RE, Bower MR, Martin RC. Hepatic resection for colorectal liver metastases. *Surg Clin North Am* 2010; **90**: 839–52.
52. Fitzgerald TL, Brinkley J, Banks S, *et al.* The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review. *Langenbecks Arch Surg* 2014; **399**: 989–1000.
53. Quan D, Gallinger S, Nhan C, *et al.* The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. *Surgery* 2012; **151**: 860–70.
54. Schiergens TS, Rentsch M, Kasparek MS, *et al.* Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases. *Dis Colon Rectum* 2015; **58**: 74–82.
55. Adam R, Frilling A, Elias D, *et al.* Liver resection of colorectal metastases in elderly patients. *Br J Surg* 2010; **97**: 366–76.
56. Schneider CP, Fertmann J, Geiger S, *et al.* Long-term survival after surgical critical illness: the impact of prolonged preceding organ support therapy. *Ann Surg* 2010; **251**: 1145–53.

Thirty-day mortality leads to underestimation of postoperative death after liver resection: A novel method to define the acute postoperative period

Tobias S. Schiergens, MD,[a] Maximilian Dörsch, MD,[a] Laura Mittermeier, MSc,[b] Katharina Brand, MSc,[b] Helmut Küchenhoff, PhD,[b] Serene M. L. Lee, PhD,[a] Hao Feng, MD,[a] Karl-Walter Jauch, MD,[a] Jens Werner, MD,[a] *and* **Wolfgang E. Thasler, MD,[a]** *Munich, Germany*

Background. *Postoperative mortality commonly is defined as death occurring within 30 days of surgery or during hospitalization. After resection for liver malignancies, this definition may result in underreporting, because mortality caused by postoperative complications can be delayed as the result of improved critical care. The aim of this study was to estimate statistically the acute postoperative period (APP) after partial hepatectomy and to compare mortality within this phase to standard timestamps.*
Methods. *From a prospective database, 784 patients undergoing resection for primary and secondary hepatic malignancies between 2003 and 2013 were reviewed. For estimation of APP, a novel statistical method applying tests for a constant postoperative hazard was implemented. Multivariable mortality analysis was performed.*
Results. *The APP was determined to last for 80 postoperative days (95% confidence interval 40–100 days). Within this period, 55 patients died (7.0%; 80-day mortality). In comparison, 30-day mortality (*N = *32, 4.0%) and in-hospital death (*N = *39, 5.0%) were relevantly less. No patient died between postoperative days 80 and 90. The causes of mortality within 30 days and from days 30–80 did not greatly differ, especially regarding posthepatectomy liver failure (44% vs 39%,* P = *.787). Septic complications, however, tended to cause late deaths more frequently (43% vs 25%,* P = *.255). Comorbidities (Charlson comorbidity index ≥3;* P = *.046), increased preoperative alanine aminotransferase activity (*P = *.030), and major liver resection (*P = *.035) were independent risk factors of 80-day mortality.*
Conclusion. *After liver resection for primary and secondary malignancies, 90-day rather than 30-day or in-hospital mortality should be used to avoid underreporting of deaths. (Surgery 2015;158:1530-7.)*

From the Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery,[a] Hospital of the University of Munich; and Department of Statistics,[b] Ludwig-Maximilians-University, Munich, Germany

An increasing number of patients are considered for operative treatment of malignant liver lesions because resection remains the best and only potentially curative therapeutic option. As diagnostic and operative techniques as well as perioperative care have markedly improved during the last several decades, the rate of resections will continue to increase.[1,2] Furthermore, criteria for surgery have been expanded greatly towards a more aggressive approach, especially for liver metastases.[2,3] As a consequence, it is crucial to consider perioperative mortality when obtaining informed consent and evaluating individual risks and benefits of liver surgery. In this context, operative mortality traditionally has been reported as death within 30 days after surgery or during hospitalization[1,3-15]; however, 30-day, 90-day, and in-house-mortality rates used to indicate early procedural outcome after liver resection have been published nonuniformly, which hinders the interpretation and comparison of mortality rates and risk factors. Careful patient selection on the basis of outcome

Accepted for publication July 4, 2015.

Reprint requests: Wolfgang E. Thasler, MD, Professor of Surgery, Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Hospital of the University of Munich, Marchioninistr. 15, D-81377 Munich, Germany. E-mail: wolfgang.thasler@med.lmu.de.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.07.019

predictors is the key for decreasing postoperative death.[13] On the basis of individual observations, some studies have found that 90-day mortality rates after liver resection[16] or other major abdominal surgery[4] are clearly greater than 30-day mortality rates, which may be attributable to improvements in critical care that delay death to beyond 30 days after surgery.[4] Furthermore, deaths related to liver resection also can occur after hospital discharge. These findings indicate the necessity of defining precisely the acute postoperative period (APP) in this patient population so that mortality rate and risk factors of mortality are reported in a proper and standardized manner. A scientific assessment of the duration of the APP based on precise statistical analysis, however, has not yet been performed.

Thus, the aim of the present study was to define precisely the APP after resection of primary and secondary malignant liver tumors by applying novel statistical analyses. This study also compared the mortality rate observed during the statistically determined APP to the 30-day and in-hospital mortality rates.

PATIENTS AND METHODS

Design, study population, and data assessment. Data of patients undergoing elective liver resection with curative intent between 2003 and 2013 were collected prospectively. This study was approved by the Ethics Committee, Faculty of Medicine, Ludwig-Maximilians-University. The study design, data acquisition, statistical methods, and manuscript preparation were carried out following the STROBE guidelines.[17] For prospective standardized data assessment, electronic case report forms were used as reported previously.[18] Comorbidities were stratified using the classification of the American Association of Anesthesiologists as well as the Charlson comorbidity index.[19] The type of liver resection was classified using the Brisbane nomenclature.[20] Steatosis, fibrosis, and cirrhosis were assessed systematically by gross and microscopic pathology. Steatosis was defined as the presence of at least 5% steatotic hepatocytes.[21] Major resection was defined as hemihepatectomy or extended hemihepatectomy. Postoperative complications were assessed according to the validated Clavien-Dindo classification.[22] Posthepatectomy liver failure (PHLF) was defined according to the definition by the International Study Group of Liver Surgery.[23] Thirty-day and in-hospital mortalities as well as death within the statistically calculated APP were assessed.

Statistical analysis. The R-language (version 3.1.0, Vienna 2014) and SPSS (version 22.0; IBM, Armonk, NY) were used for the statistical analysis. Binominal variables are expressed as numbers and percentages, and continuous variables are expressed as medians and ranges [minimum and maximum] or means ± standard deviation. For comparison, the χ^2 test or Fisher exact test (expected frequency <5) was used depending on the character of the variable. In addition, to compare risk factors associated with mortality occurring within the APP in our population to those identified in populations of previously published studies, univariable and multivariable regression was performed. For multivariable analysis, variables were entered into a hierarchical stepwise logistic regression analysis.

For estimation of the APP, the transition point t between the acute and postacute postoperative phase was statistically assessed. From the postoperative daily hazard rate of the entire study population which indicates the probability to die on the next day (the Figure), the day t after surgery was identified, beyond which the hazard rate became constant (transition or change point). Thus, t indicated the beginning of the postacute phase. For this purpose, we used a method for change point estimation based on data of threshold estimation published by Mallik et al.[24] The hazard rate h_1 was assumed to be constant beyond one year after surgery and was estimated based on the overall survival data of the study population. Subsequently, a series of tests for the hazard rate being equal to h_1 at intervals of 20 days was conducted. This was performed by a binomial test using the number of persons at risk and the number of surviving patients. This resulted in a series of P values for intervals from 20 to 40 days to 340–360 days. Prior to the change point (acute phase), significantly greater hazards for the intervals are assumed (small corresponding P-values), whereas after t (postacute phase), no significance for intervals would be assumed (high corresponding P-values). Thereby, the transition point t could be estimated from this series of P-values. The 95% confidence interval (95% CI) was calculated using the nonparametric bootstrap method. The method's performance was validated within a parallel statistical simulation study (data not shown).

RESULTS

Patient population. Between 2003 and 2013, 1,032 patients underwent resection of benign and malignant liver tumors. None of the patients with benign tumors ($N = 95$) died within 90 days after surgery, and this population was excluded from the analysis. After further exclusion of 153 patients because of incomplete case report forms,

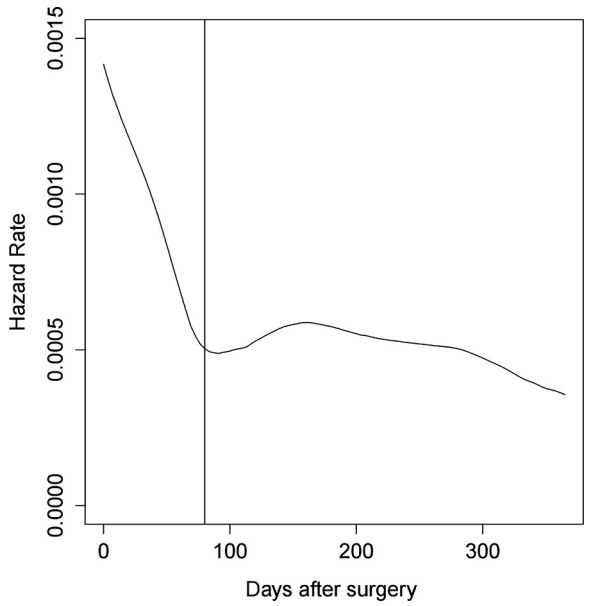


Fig. Based on the smoothed, unadjusted daily hazard rate of the entire population of 784 patients, the transition point *t* between the exponential (acute phase) and constant intervals (postacute period) was calculated. The acute phase shows a rapidly decreasing hazard rate, whereas the postacute period is characterized by a constant rate. A time-dependent series of statistical tests showed that *t* was day 80 after surgery (95% confidence interval 40–100d).

784 cases were included in the present study and were used to determine the long-term daily hazard function entire study population; the Figure. Sixteen patients were lost to follow-up within 80 days after operation (2%), 47 within the first year after surgery (6%) with a median follow-up of 137 days. The median follow-up of the entire study population was 27 [0–125] months. The patients' clinical and perioperative characteristics are displayed in Table I. The median overall survival of the population was 48 months, with a 5-year survival rate of 43%.

Acute postoperative period and mortality rates. Exploration of the hazard function indicated that the APP to lasted for 80 days after resection, with a 95% CI of 40–100 days (Figure). Within the APP, 55 patients died (7.0%; 80-day mortality). The rates of 30-day mortality (N = 32, 4.0%) and in-hospital death (N = 39, 5.0%) were relevantly less. Sixteen patients (2.0%) died after discharge within 80 postoperative days. There was no in-hospital death after postoperative day 80. Twenty-three patients (2.9%) died between postoperative days 30 and 80 (conditional 80-day mortality). No patients died intraoperatively. The median time to death after resection among the 80-day mortality subpopulation was 21 days. The primary causes of postoperative death are shown in Table II. Finally, most patients died at the intensive care unit from multisystem organ failure that was caused by the complications reported in Table II. The frequencies of the different underlying causes of mortality were not significantly different between the 30-day and conditional 80-day mortality subpopulations, especially for PHLF (44% vs 39%, P = .787). Although statistically insignificant, sepsis without PHLF (43% vs 25%, P = .255) and respiratory failure (17% vs 3%, P = .149), most frequently because of pneumonia, tended to cause more frequently late, whereas cerebrovascular events (especially postoperative myocardial infarction; 16% vs 4%, P = .383) and postoperative intra-abdominal hemorrhage (9% vs 0%, P = .257) tended to be associated with earlier death after resection. No patient died from cancer progression within the first 100 days after surgery.

Mortality regression analysis. The univariable 80-day mortality regression analysis is presented in Table I. The final multivariable regression model calculated as described previously is shown in Table III. We identified a Charlson comorbidity score ≥3 (presence of more than 2 comorbidities or of more than 1 severe comorbidity), increased preoperative serum alanine aminotransferase (ALT) activity, and major liver resection as independent risk factors of 80-day mortality. A 30-day mortality analysis also was conducted and had the same risk factors in the final model; however, the only statistically significant factor was a Charlson comorbidity score ≥3 (data not shown).

DISCUSSION

Based on the daily hazard rate of the entire population of 784 patients, the APP was found to last for 80 days after liver resection for primary and secondary malignancies. The 80-day mortality rate was relevantly greater than the 30-day and in-hospital mortality rates. Although the primary causes of postoperative death within the first 30 days after surgery and between postoperative days 30 and 80 did not differ significantly, septic complications tended to cause late deaths more frequently, whereas cerebrovascular events and abdominal hemorrhage tended to be associated with earlier mortality. Comorbidities, increased preoperative serum ALT level, and major resection were identified as independent risk factors of 80-day mortality.

In the light of advancements in diagnostics, surgical techniques, and perioperative care, the criteria for resection for a wide range of liver

Table I. Patients' clinical characteristics and univariable analysis of 80-day mortality

Variable	*No. of patients (%)*	*80-day mortality,* P *value*[*]
No. patients	784 (100)	
Age at resection, yr	64.0 [18–96][†]	<.001
Sex		.318
Female	321 (45)	
Male	463 (55)	
Diagnosis		.032
Primary malignancy	307 (39)	
Metastases	477 (61)	
Primary malignancies		
Hepatocellular carcinoma	169 (22)	
Cholangiocarcinoma	79 (10)	
Klatskin tumor	38 (5)	
Gallbladder carcinoma	21 (2)	
Metastases		
Colorectal, synchronous[‡]	102 (13)	
Colorectal, metachronous	194 (25)	
Neuroendocrine	23 (3)	
Noncolorectal, non-neuroendocrine	158 (20)	
Comorbidities		
ASA >2	508 (65)	.204
CCI ≥3	138 (18)	.002
Previous chemotherapy	286 (41)	.054
Liver disease		
Steatosis	372 (47)	.387
Fibrosis	181 (23)	.363
Cirrhosis	78 (10)	.287
BChE activity [kU/L, 37 °C][§]	7.4 ± 2.1	<.001
AST [U/L, 37 °C][§]	53.5 ± 65.8	.001
ALT [U/L, 37 °C][§]	54.7 ± 65.8	<.001
Bilirubin [mg/dL][§]	1.2 ± 2.6	.490
No. of liver tumors		.310
≥3	141 (18)	
2	142 (18)	
1	501 (64)	
(Extended) hemihepatectomy	261 (33)	.002
Pringle maneuver	175 (22)	.668
Blood loss >1,000 mL	199 (25)	<.001
Perioperative transfusion	293 (37)	<.001
Severe complications	246 (31)	<.001
Operative complications[¶]		<.001
Secondary hemorrhage	25 (3)	
Abscess	36 (5)	
Bile leak/bilioma	61 (8)	
Wound infection	54 (7)	
Nonoperative complications		<.001
Acute coronary syndrome	56 (7)	
Respiratory failure	85 (11)	
Pneumonia	32 (4)	
PHLF	60 (8)	
Total HLOS ≥12 d	406 (52)	.482
ICU LOS ≥2 d	142 (18)	<.001
Readmission to the ICU	47 (6)	<.001
Intraoperative mortality	0 (0)	
30-day mortality	32 (2)	
80-day mortality	55 (7)	

(*continued*)

Table I. (*continued*)

Variable	*No. of patients (%)*	*80-day mortality,* P *value*[*]
Conditional 80-day mortality[**]	23 (3)	
In-hospital mortality	39 (5)	
80-day mortality after discharge[††]	16 (2)	

*Univariable regression analysis of 80-day mortality.
†Numbers as median and [range].
‡Assessed before or within 3 months after primary tumor resection.
§Numbers as mean ± standard deviation.
¶Clavien-Dindo > II.
**Death occurring between day 30 and 80.
††Death occuring between hospital discharge and postoperative day 80.
ASA, American Association of Anesthesiologists; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *BChE*, plasma pseudocholinesterase; *CCI*, Charlson comorbidity index; *HLOS*, hospital length of stay; *ICU*, intensive care unit; *PHLF*, posthepatectomy liver failure.

Table II. Primary causes of mortality

Cause of mortality	*30-day mortality,* n *(%)*	*Cond. 80-day*[*] *mortality,* n *(%)*	*80-day mortality,* n *(%)*	P *value*[†]
No. of patients	32 (100)	23 (100)	55 (100)	
PHLF	14 (44)	9 (39)	23 (42)	.787
Sepsis[‡]	8 (25)	10 (43)	18 (33)	.255
Respiratory failure	1 (3)	4 (17)	5 (9)	.149
Cerebrovascular event	5 (16)	1 (4)	6 (11)	.383
Abdominal hemorrhage	3 (9)	0 (0)	3 (5)	.257

*Deaths occurring between day 30 and day 80 after resection.
†30-day vs cond. 80-day mortality.
‡Without associated liver failure.
PHLF, Posthepatectomy liver failure.

Table III. Multivariable analysis of 80-day mortality

Risk factor	P *value*	*OR*	*95% CI*
Charlson Index ≥3	.046	2.19	1.01–4.72
Increased ALT[*]	.030	2.54	1.10–5.88
Major resection	.035	2.27	1.06–4.87

*>30 U/L (37°C).
ALT, Alanine transaminase; *CI*, confidence interval; *OR*, odds ratio.

tumors have expanded, and an increasing number of patients undergo partial hepatectomy for primary liver tumors and hepatic metastases.[13] As a result of those improvements, postoperative mortality rates have decreased over the last decades.[1,8,14,25] Patient safety is clearly the greatest concern of surgeon. Therefore, in addition to long-term prognosis, precise definition of the APP and consistent evaluation of postoperative death rates is of great interest. This would allow for the identification of risk factors and, thus, the estimation of procedural risk as well as the stratification of patients into risk categories. This, in turn, could significantly improve patient selection. Despite reports of improved mortality rates to less than 6% at large volume centers, identification of patients with increased procedural risks is still necessary.[1,8,12] Previously identified mortality predictors include advanced age,[3,12,13,16,18,25-28] male sex,[1,3,27] neoplasm type,[13,26,27] pre-existing comorbidities,[1,12-14,26-30] parenchymal liver disease,[1,3,25,26] extent of resection,[3,12-14,16,25,26,28] increased blood loss,[25,30] need for blood transfusion,[3,16,30] and hospital volume.[3,12,13,28] The results of our analysis support those previous findings; we identified comorbidities, underlying liver disease, and major liver resection as independent risk factors of 80-day mortality (Table III). Furthermore, our regression model closely corresponds with the preoperative risk score of Simons et al.[12] Among the preoperative liver function tests, pseudocholinesterase activity as well as aspartate and alanine transaminase activity was univariably associated with 80-day mortality. Steatosis, fibrosis, and cirrhosis that were histopathologically assessed did not significantly increase the odds of mortality. This might be explained by a high number ($N = 257$) of mild forms of steatosis defined as the presence of 5–33% steatotic hepatocytes and a stringent patient selection. The high prevalence of steatosis (47%)

may have resulted from a relevant number of patients who had received preoperative chemotherapy[31,32] (41%) and a high methodological sensitivity due to systematic histopathological examination of all samples and the low, but well-established cut-off of 5% steatotic hepatocytes.[21]

In the literature, APP after liver resection is reported nonuniformly as 30-day,[1,5,6,10,11,16,33] in-hospital,[3,8,9,12,13] and 90-day mortality.[2,16,26,27,34,35] This significantly confounds the comparability of those data. In addition, regression models with 30-day cut-offs may be statistically underpowered. After liver resection, 90-day mortality has been shown to be markedly greater than 30-day mortality.[16] Hyder et al[2] reported that 22% of patients who died within postoperative 90 days did so after hospital discharge. Recently, Swanson et al[4] showed that the 90-day mortality rate after pancreatectomy is double that of the 30-day rate underlining the importance of reporting 90-day mortality after major abdominal operations.

For liver surgery, however, the exact length of APP is still unclear, and a statistical approach to determine this acute phase had not been undertaken. In the current study, by assessing the hazard rate of a population of 784 resections of liver malignancies, we determined that the population's hazard rate is not constant before 80 days after surgery. Our method provides a scientific foundation for determining acute hazard periods in large populations with sufficient follow-up. In this context, we demonstrated relevant differences in 30-day and inpatient mortality rates compared with that at day 80. This is underlined by the fact that postoperative day 30 was found to be outside the 95% confidence interval of our statistical APP. Between days 80 and 90, no patient in our cohort died. Thus, our transition point calculation of 80 days supports the suitability of using 90 days as the best established cut-off.

For the first time, a scientific foundation is provided that postoperative day 30 is not the end of the mortality period. Our data remove any basis for choosing 30-day mortality and demonstrate that this results in underestimation and bias. We therefore would espouse to report 90-day mortality, because this is an already-established cut-off after major hepatobiliary and other abdominal surgery. In turn, studies excluding patients with perioperative mortality to analyze independent long-term survival should also use 90 days as cut-off.

The effect of delayed postoperative mortality (conditional 80-day deaths) might be explained by improved perioperative intensive care with increased ability to support critically ill patients postoperatively, thereby extending the life of patients with severe complications and postponing the event of death beyond 30 days. Thus, improvements in medical care might be responsible for the reduction in all-cause mortality after partial hepatectomy, but they may also be responsible for underestimations of procedural death when the APP was considered to be only 30 days in duration. This is comprehensibly reflected by the primary mortality causes in our population. Although primary causes of death between days 30 and 80 were statistically comparable with those of patients that died prior to day 30, septic complications tended to cause late deaths more frequently whereas cerebrovascular events and abdominal hemorrhage tended to be associated with earlier deaths. Septic complications might initially or partially be treated with sufficient efficacy (ie, antibiotics or invasive intervention), but secondary treatment failure might result in delayed mortality. In contrast, fulminant myocardial infarction, pulmonary embolism, and severe postoperative bleeding tended to cause early mortality due to on primary failure of critical care. Thus, our data indicate that the type of postoperative complication and the ability of postoperative critical care management can at least partially determine the risk period of postoperative mortality.

Considering the era of modern critical care, especially in large-volume centers, taking our own data into consideration,[36] we conclude that based on our results of an APP of 80 days, 90 days as well-established cut-off should be uniformly reported and analyzed. Some limitations of the present study have to be noted. First, the calculation of the APP is based on data of a single-center cohort. Thus, our analyses are not adjusted for patient characteristics, the surgeon performing the procedure, the quality of critical care, or hospital volume. The cut-off of 80 days may vary between different patient populations due to differences in those characteristics and generalizability is therefore limited.

Furthermore, inclusion and exclusion bias in other investigations may lead to relevant shifts of the transition point and stringent exclusion criteria in randomized trials may result in an earlier transition point. In contrast, inclusion of all-comers may cause a shift towards a later point. In the light of our confidence interval of APP, however, we are convinced firmly that reporting of 30-day mortality most likely leads to relevant underestimation and bias in other patient populations, too. Furthermore, comparability of our patients' baseline characteristics, outcomes, and mortality risk

factors with other published Western patient cohorts indicates that our APP interval of 80 days might be applied to other patient populations with a certain probability. Despite the limitation of a single-center study, a multitude of prospectively assessed demographic, medical, oncological, and perioperative key factors and their impact on mortality could be analyzed in a large patient cohort. Our results indicate the necessity to calculate the APP based on data of a large multicenter population to increase the generalizability and to give a more obligatory recommendation.

Second, 16 patients (2%) were lost to follow-up within the first 80 days after operation, and 47 patients (6%) within the first year. The APP was calculated based on death events occurring in the first year. Nevertheless, the patients with incomplete follow-up within this period had a median follow-up of 137 days. Aside from a trend of increased age in the group of patients with complete follow-up ($P = .07$), there were no significant differences between patients with and without complete follow-up concerning the baseline, tumor-specific, and perioperative characteristics (data not shown). Especially with regard to mortality risk factors (Charlson comorbidity index, $P = .258$; ALT, $P = .258$; major liver resection, $P = .172$), no differences could be detected. Thus, there was no indication of a major systematic bias. Overall, a sufficient follow-up enabled calculation of a hazard function of 784 patients treated in a tertiary referral hospital with high-quality critical care of surgical patients.[36] This allowed us to precisely calculate the APP.

Third, patients with benign liver tumors had been excluded from the analysis because these patients showed significant differences in baseline characteristics, comorbidities, perioperative characteristics, and postoperative morbidity, which is well known from the literature.[5,37] Moreover, mortality after resection for benign lesions has been reported to be very low; most of the studies report no perioperative deaths.[5,37,38] Thus, exclusion of this subgroup was deliberately decided to avoid bias in APP calculation and regression analysis. On the other hand, this might have caused a certain bias by exclusion of patients with a favorable perioperative outcome. In fact, there was no postoperative mortality among our patients with benign liver tumors and no patient died within the first year which was the basis to calculate the APP. Re-calculation of the APP after inclusion of patients with benign tumors revealed identical results (transition point at day 80, 95% CI 40–100 days; data not shown).

Even in the modern era of surgery and perioperative care, liver resections for primary and secondary neoplastic disease continue to be high risk. Our results demonstrate that 90-day rather than 30-day mortality or in-hospital death should be used uniformly, because this is more consistent with the statistically calculated interval of 80 days. Furthermore, 30-day or in-hospital mortality seems to underestimate procedural deaths, especially those due to septic complications, and may therefore cause bias of risk factor analysis. Thus, our data may influence patient selection, informed consent process, and perioperative patient evaluation.

We thank Professor W. H. Hartl for his assistance with the study design as well as Dr Hans-Martin Hornung and Mrs. Gabriele Kramer for their dedicated IT-administration of the liver database. We appreciate the assistance of Professor Alessandra Brazzale, University of Padova, in the development of the statistical method.

REFERENCES

1. Virani S, Michaelson JS, Hutter MM, Lancaster RT, Warshaw AL, Henderson WG, et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. J Am Coll Surg 2007;204:1284-92.
2. Hyder O, Pulitano C, Firoozmand A, Dodson R, Wolfgang CL, Choti MA, et al. A risk model to predict 90-day mortality among patients undergoing hepatic resection. J Am Coll Surg 2013;216:1049-56.
3. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 2008;12:842-51.
4. Swanson RS, Pezzi CM, Mallin K, Loomis AM, Winchester DP. The 90-day mortality after pancreatectomy for cancer is double the 30-day mortality: more than 20,000 resections from the national cancer data base. Ann Surg Oncol 2014;21:4059-67.
5. Erdogan D, Busch OR, Gouma DJ, van Gulik TM. Morbidity and mortality after liver resection for benign and malignant hepatobiliary lesions. Liver Int 2009;29:175-80.
6. Nygard IE, Lassen K, Kjaeve J, Revhaug A. Mortality and survival rates after elective hepatic surgery in a low-volume centre are comparable to those of high-volume centres. ISRN Surg 2012;2012:783932.
7. Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Yamashita K, et al. Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. J Am Coll Surg 2010;211:443-9.
8. Dimick JB, Cowan JA Jr, Knol JA, Upchurch GR Jr. Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. Arch Surg 2003;138:185-91.
9. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc 2005;53:424-9.

10. Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after major hepatectomy in elderly patients. J Am Coll Surg 2006;203:677-83.
11. Aldrighetti L, Arru M, Caterini R, Finazzi R, Comotti L, Torri G, et al. Impact of advanced age on the outcome of liver resection. World J Surg 2003;27:1149-54.
12. Simons JP, Ng SC, Hill JS, Shah SA, Bodnari A, Zhou Z, et al. In-hospital mortality for liver resection for metastases: a simple risk score. J Surg Res 2009;156:21-5.
13. Simons JP, Hill JS, Ng SC, Shah SA, Zhou Z, Whalen GF, et al. Perioperative mortality for management of hepatic neoplasm: a simple risk score. Ann Surg 2009; 250:929-34.
14. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191:38-46.
15. Shubert CR, Habermann EB, Truty MJ, Thomsen KM, Kendrick ML, Nagorney DM. Defining perioperative risk after hepatectomy based on diagnosis and extent of resection. J Gastrointest Surg 2014;18:1917-28.
16. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854-62.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-7.
18. Schiergens TS, Stielow C, Schreiber S, Hornuss C, Jauch KW, Rentsch M, et al. Liver resection in the elderly: significance of comorbidities and blood loss. J Gastrointest Surg 2014;18: 1161-70.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
20. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg 2005;12:351-5.
21. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology 2003;37:1202-19.
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
23. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
24. Mallik A, Sen B, Banerjee M, Michailidis G. Threshold estimation based on a p-value framework in dose-response and regression settings. Biometrika 2011;98:887-900.
25. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406.
26. Chang CM, Yin WY, Su YC, Wei CK, Lee CH, Juang SY, et al. Preoperative risk score predicting 90-day mortality after liver resection in a population-based study. Medicine (Baltimore) 2014;93:e59.
27. Reddy SK, Barbas AS, Turley RS, Gamblin TC, Geller DA, Marsh JW, et al. Major liver resection in elderly patients: a multi-institutional analysis. J Am Coll Surg 2011;212:787-95.
28. Simons JP, Ng SC, Hill JS, Shah SA, Zhou Z, Tseng JF. In-hospital mortality from liver resection for hepatocellular carcinoma: a simple risk score. Cancer 2010;116:1733-8.
29. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg 2006;243:373-9.
30. Wei AC, Tung-Ping PR, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. Br J Surg 2003;90:33-41.
31. Anderson CD, Chari RS. Chemotherapy liver injury. Surgery 2010;147:195-6.
32. Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860-8.
33. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 2006;203:865-77.
34. Motoyama H, Kobayashi A, Yokoyama T, Shimizu A, Sakai H, Furusawa N, et al. Impact of advanced age on the short- and long-term outcomes in patients undergoing hepatectomy for hepatocellular carcinoma: a single-center analysis over a 20-year period. Am J Surg 2015;209:733-41.
35. Melloul E, Halkic N, Raptis DA, Tempia A, Demartines N. Right Hepatectomy in Patients over 70 Years of Age: An Analysis of Liver Function and Outcome. World J Surg 2012;36:2161-70.
36. Schneider CP, Fertmann J, Geiger S, Wolf H, Biermaier H, Hofner B, et al. Long-term survival after surgical critical illness: the impact of prolonged preceding organ support therapy. Ann Surg 2010;251:1145-53.
37. Kamphues C, Engel S, Denecke T, Bova R, Hippler-Benscheidt M, Puhl G, et al. Safety of liver resection and effect on quality of life in patients with benign hepatic disease: single center experience. BMC Surg 2011;11:16.
38. Ibrahim S, Chen CL, Wang SH, Lin CC, Yang CH, Yong CC, et al. Liver resection for benign liver tumors: indications and outcome. Am J Surg 2007;193:5-9.

Histomorphologic and molecular phenotypes predict gemcitabine response and overall survival in adenocarcinoma of the ampulla of Vater

Tobias S. Schiergens, MD,[a,b] Simone Reu, MD,[b,c] Jens Neumann, MD,[b,c] Bernhard W. Renz, MD,[b,d] Hanno Niess, MD,[a,b] Stefan Boeck, MD,[b,e] Volker Heinemann, MD,[b,e] Christiane J. Bruns, MD,[f] Karl-Walter Jauch, MD,[a,b] *and* **Axel Kleespies, MD,[a,b]** *Munich and Magdeburg, Germany, and New York, NY*

Background. *The need for adjuvant chemotherapy after resection of ampullary cancer (PapCa) remains undefined. Recent data suggest that a different epithelial origin of PapCa might be associated with different tumor biology. The aim of the present study was to assess the clinical value of morphologic and immunohistochemic subclassification of PapCa into intestinal-type (IT) and pancreaticobiliary-type (PT) to predict chemotherapy response and overall survival (OS).*

Methods. *Via a prospective database, 112 PapCa were identified, of which 95 could be included in the present study. Those were compared with 206 matching patients with periampullary pancreatic cancer (ie, pancreatic ductal adenocarcinoma, PDAC). IT and PT PapCa were classified morphologically, and tissue microarray was prepared with immunohistochemistry for CK7, CK20, MUC2, CDX2, β-Catenin, and Villin. Multivariate survival analysis was performed.*

Results. *OS of PT patients was less compared with IT patients (25 vs 98 months;* $P < .001$*), whereas it was comparable with patients with PDAC (25 vs 14 months;* $P = .123$*). PT patients receiving adjuvant gemcitabine chemotherapy featured improved OS (32 vs 13 months;* $P = .013$*), whereas gemcitabine tended to be associated with decreased OS in IT patients (35 vs 112 months;* $P = .193$*). Besides histopathologic classification, expression of CK7 and MUC2 were important prognostic variables. PT patients with CK7-positivity or MUC2-negativity were segregated into an even poorer prognostic group.*

Conclusion. *PapCa is not a separate tumor entity. We demonstrate important differences between IT-PapCa and PT-PapCa not only in long-term survival but also in response to adjuvant gemcitabine. Tumor biology and clinical course of PT tumors resemble those of PDAC. PT tumors should therefore be treated like PDAC. (Surgery 2015;158:151-61.)*

From the Department of General-, Visceral-, Transplantation-, Vascular- and Thoracic Surgery,[a] Pancreatic Cancer Center Munich[LMU,b] and Department of Pathology,[c] University of Munich, Munich, Germany; Division of Digestive and Liver Diseases,[d] Irving Cancer Research Center, Columbia University Medical Center, New York, NY; Department of Medical Oncology,[e] University of Munich, Munich; and Department of General-, Visceral- and Vascular Surgery,[f] University of Magdeburg, Magdeburg, Germany

Accepted for publication February 3, 2015.

Reprint requests: Axel Kleespies, MD, Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, University of Munich - Campus Grosshadern, Marchioninistr. 15, D-81377 Munich, Germany. E-mail: axel.kleespies@med.lmu.de.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.02.001

The prognosis of patients with carcinoma of the ampulla of Vater (PapCa) is far better than that of those with ductal adenocarcinoma of the pancreatic head (ie, pancreatic ductal adenocarcinoma; PDAC)[1-3] because their symptoms might appear earlier in the course of the disease.[2] Because the ampulla of Vater represents a boundary between different epithelia, the biology of tumors arising from this border may differ according to varying

genuine tumor origin (duodenal, biliary, or ductal pancreatic epithelia) and may thereby influence patients' clinical outcome.[4,5] Indeed, among patients with PapCa, there is a broad interindividual range of outcomes that impairs the prediction of specific outcomes and clinical decision making as to individual adjuvant therapy.[6-11] Kimura et al[12] suggested to subdivide PapCa into intestinal type (IT) and pancreaticobiliary type (PT) emphasizing those as main tumor "subtypes." Histologically, IT PapCa resemble tumors of intestine, whereas PT PapCa are similar to PDACs and those of extrahepatic bile ducts. This classification is performed on the basis of morphology.[4,11,12] Studies have suggested differences in tumor biology[2,11]; however, results have been contradictory probably because of the infrequency of this entity.[12-18] Furthermore, therapeutic implications of this stratification and its clinical utility have not been shown. Notably, suitability for predicting chemotherapy response has not been assessed.

Our aim was to investigate the outcome of a large, single-center population with PapCa who were undergoing partial pancreaticoduodenectomy compared with matched patients with periampullary PDAC. To the best of our knowledge, this is the first study to assess the clinical utility of histomorphologic and molecular classification of PapCa into IT and PT to predict chemotherapy response, hereby enabling decision making for tailored adjuvant therapy.

PATIENTS AND METHODS

Design and study population. The study was approved by the local Ethics Committee. Design, data-acquisition, statistical methods, and manuscript preparation were carried out according to Strengthening the Reporting of Observational Studies in Epidemiology (ie, STROBE) guidelines.[19] From the prospective database of the local pancreatic cancer center, which included 2,165 pancreatic surgeries, patients undergoing pancreatoduodenectomy (PD) between 1991 and 2012 for PapCa were identified (Fig 1). PapCa was defined as tumors primarily located in the ampulla of Vater, which was determined as previously reported.[6]

To define the origin, the epicenter of adenocarcinoma was assessed grossly and microscopically, and tumor components were evaluated carefully for the localization of an in situ carcinoma as well as the involvement of the papilla-of-Vater mucosa. Tumors with their epicenter in the ampullary region but sparing the mucosa of the papilla were excluded just

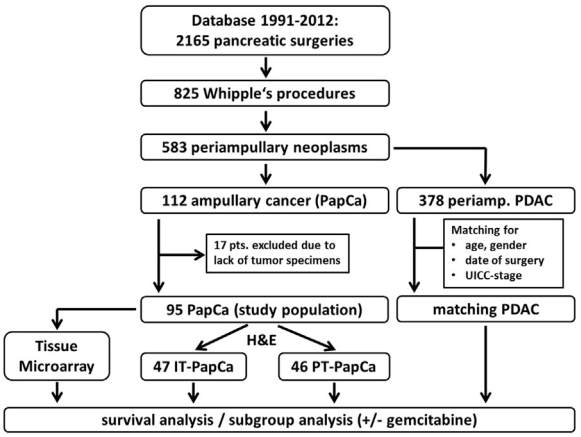


Fig 1. Study profile. Evaluation of more than 2,000 consecutive pancreatic surgeries revealed 112 PapCa patients. Of those, 95 were included in the present study and featured sufficient follow-up and tumor specimens for tissue microarray. For a matched analysis, patients with periampullary pancreatic ductal adenocarcinoma (PDAC) matching sex, age, date of surgery, and Union for International Cancer Control (UICC) stage were identified.

as those originating from the distal common bile duct or those with the main tumor mass outside the papilla. For comparison of survival, patients undergoing PD for periampullary PDAC were matched separately to those with PapCa and to the PT subgroup of PapCa, respectively (Fig 1 and Fig 2, *A* and *C*). Matching criteria were sex, age (±5 years), date of surgery (±5 years), and Union for International Cancer Control stage.[20] Comorbidities were stratified applying the classification according to the American Society of Anesthesiologists. Postoperative complications were assessed according to the validated Clavien-Dindo classification.[21] Patients underwent close outpatient follow-up at 3- and 6-month intervals. Overall survival (OS) was determined from date of surgery to date of death or last recall.

Histopathologic evaluation based on morphology. Histopathologic stratification of PapCa into IT and PT was carried out double-blinded on the basis of hematoxylin and eosin (H&E) stains of representative formalin fixed paraffin-embedded tissue specimen by 2 independent pathologists (S.R. and J.N.) according to criteria previously reported.[4,5,15] In brief, IT-PapCa was defined by tubular to elongated glands, cribriform, or solid nests of columnar cells with pseudostratified nuclei closely resembling colorectal adenocarcinoma (Fig 2, *F*). PT-PapCa consists of simple or branching glands as well as solid nests of mainly cuboidal cells with a high

degree of nuclear pleomorphism surrounded by striking desmoplastic stroma (Fig 2, *E*).[2] Mixed-type tumors were classified according to their predominant component. Mucinous adenocarcinomas were considered as variants of IT according to the current World Health Organization classification.[22] Discrepancies were resolved by a subsequent consensus decision.

Tissue microarray (TMA) and biomarkers. For TMA preparation, sections of tumor tissue containing paraffin blocks were screened and representative areas of tumor were marked.[23] By the use of a hollow needle (Beecher Instruments, Sun Prairie, WI), three 1.0-mm tissue cores were punched out of regions of interest, respectively. They were reinserted in triplicates in a recipient paraffin block in a precisely spaced array pattern. Five-micrometer serial sections of these blocks were cut. Staining with primary monoclonal mouse antibodies against antigens of PT (CK7) and IT (CK20, MUC2, CDX2, ß-catenin, Villin) was performed on a Ventana Benchmark XT autostainer (Ventana Medical Systems, Inc, Tucson, AZ) following the manufacturer's instructions. Results were evaluated double-blinded by S.R. and J.N., and staining was scored semiquantitatively as previously published[11]: No expression (0); weak expression (I); intermediate expression (II); and strong expression (III). Scores II and III were considered as positive (+) for CK7 and CK20, I-III for MUC2, CDX2, ß-catenin, and Villin. Staining of single cells was considered as negative. For β-catenin, only nuclear staining was assessed.

Statistical analysis. Continuous variables are given as median [range] and categorical variables as number (percentage). For comparison of variables between IT and PT, Mann-Whitney *U* test, χ^2 test, or Fisher exact test were used depending on the variable. Univariate survival analysis was estimated applying Kaplan-Meier statistics. Statistical differences were assessed by the log-rank test. The number of patients at risk illustrated by Kaplan-Meier survival estimator was truncated when it was less than one-third of the starting figure. The Cox proportional hazard model was applied for multivariate survival analyses including factors that were associated with OS and that were related to histopathologic subtype. A *P*-value of less than .050 (2-sided) was regarded as statistically significant. For statistical analyses, SPSS (version 20.0, IBM, Chicago, IL) was used.

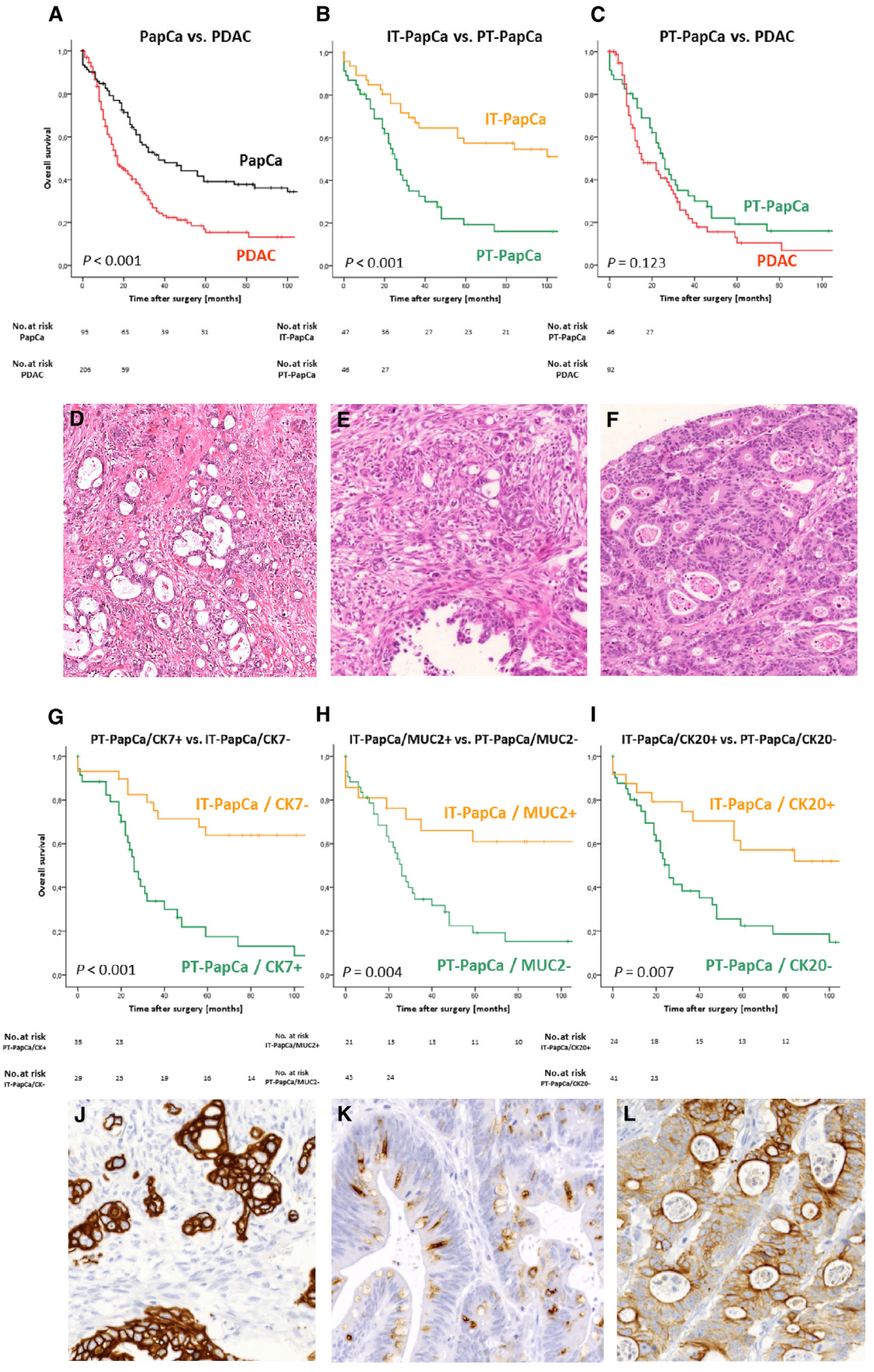
RESULTS

Patient population and stratification. From our prospective database, 95 patients undergoing partial pancreaticoduodenectomy for PapCa with sufficient tumor specimens were identified (Fig 1). Median follow-up was 32 months [0–256], whereat 63 patients (68%) had deceased at the end of the study. Histopathologic stratification of tumor specimen revealed 47 IT-PapCa (49%), 46 PT-PapCa (48%), and 2 undifferentiated PapCa (G4). In 9 samples (9.5%), discrepancies between histopathologic stratification mostly due to mixed patterns necessitated a consensus decision. For comparison, 206 patients with PDAC meeting the matching criteria for PapCa (follow-up: 11 months [0–142]) and 92 patients with PDAC for PT-PapCa (follow-up: 10 months [0–142]) were identified, respectively.

Patients' clinical characteristics. Patients' clinical characteristics are presented in Table I. The groups of IT and PT patients were similar with regard to patient numbers, demographics, as well as preoperative risk (American Society of Anesthesiologists classification), symptoms, and interventions. Moreover, type and extent of surgery, duration of the operation, postoperative complications, and hospital duration of stay were comparable. PT-PapCa, however, were assessed more frequently at advanced pT- and pN-stages (pT3/4: 65% vs 40%, $P = .022$; pN+; 67% vs 28%, $P < .001$) and tended to show more high-grade tumors (G3/4; 57% vs 38%, $P = .060$).

Mortality and long-term survival. Thirty-day-mortality did not differ between the PT and IT groups of patients (5% vs 3%, *P* .486). Postoperative median survival of PapCa and matched PDAC patients, however, was 37 and 17 months ($P < .001$), and of IT- and PT-PapCa 98 and 25 months, respectively ($P < .001$). PDAC patients matched with PT-PapCa had a median OS of 14 months. Kaplan-Meier plots are shown in Fig 2; 1-, 5-, and 10-year survival rates were 85%, 57%, and 43% for IT patients, 78%, 19%, and 11% for PT patients, and 64%, 17%, 8% for PDAC patients matched with PapCa, respectively. Comparing the Kaplan-Meier plot of PT patients with that of PDAC patients, we found that the curves closely resemble each other (Fig 2, *C*).

Multivariate survival analysis. Analysis of risk factors is presented in Table II. With regard to general risk factors, age >65 years was univariately, but not multivariately associated with reduced OS ($P = .059$). Severe postoperative complications (Clavien-Dindo >grade II) independently decreased OS ($P < .001$). Pancreaticobiliary differentiation of PapCa (H&E staining, PT), however, represented the strongest independent oncologic risk factor for reduced OS when we adjusted for nodal involvement and advanced pT-stages. Nodal metastases (pN+)


A
PapCa vs. PDAC
Overall survival
PapCa
PDAC
P < 0.001
Time after surgery [months]
No. at risk PapCa 95 63 39 31
No. at risk PDAC 206 59
B
IT-PapCa vs. PT-PapCa
IT-PapCa
PT-PapCa
P < 0.001
Time after surgery [months]
No. at risk IT-PapCa 47 36 27 23 21
No. at risk PT-PapCa 46 27
C
PT-PapCa vs. PDAC
PT-PapCa
PDAC
P = 0.123
Time after surgery [months]
No. at risk PT-PapCa 46 27
No. at risk PDAC 92
D
E
F
G
PT-PapCa/CK7+ vs. IT-PapCa/CK7-
Overall survival
IT-PapCa / CK7-
PT-PapCa / CK7+
P < 0.001
Time after surgery [months]
No. at risk PT-PapCa/CK+ 35 23
No. at risk IT-PapCa/CK- 29 25 19 16 14
H
IT-PapCa/MUC2+ vs. PT-PapCa/MUC2-
IT-PapCa / MUC2+
PT-PapCa / MUC2-
P = 0.004
Time after surgery [months]
No. at risk IT-PapCa/MUC2+ 21 15 13 11 10
No. at risk PT-PapCa/MUC2- 43 24
I
IT-PapCa/CK20+ vs. PT-PapCa/CK20-
IT-PapCa / CK20+
PT-PapCa / CK20-
P = 0.007
Time after surgery [months]
No. at risk IT-PapCa/CK20+ 24 18 15 13 12
No. at risk PT-PapCa/CK20- 41 23
J
K
L

also emerged as an independent prognostic factor ($P = .025$), whereas pT-stage (pT3/4) and tumor-grade (G3/4) had no prognostic value.

TMA and prognostic value. For TMA, 85 tumor samples (42 IT-PapCa, 43 PT-PapCa) could be analyzed by immunohistochemistry, whereas TMA-cores of 10 specimens lacked sufficient staining quality being therefore excluded from immunophenotypic evaluation. From all markers assessed, MUC2 (88%; Fig 2, *K*) and CK20 (83%; Fig 2, *L*) proved to have the best positive predictive values in relation to the morphological "gold standard" classification (H&E). CK7 showed the greatest sensitivity (81%) of all markers evaluated (data of all markers available as Supplementary Tables I and II). Table III shows the morphologic classification, different immunophenotypes, and their combinations as prognostic factors. CK7 (hazard ratio [HR] 1.86) and MUC2 (HR 0.51) were identified as prognostic markers on their own. Compared with morphologic classification (HR 2.38), however, none of the markers proved to be a better prognostic factor on its own (Table III). Creating intersections, we found that PT patients with additional CK7 expression (HR 3.37; Fig 2, *G* and *J*) or lack of MUC2 (HR 2.73; Fig 2, *H*) were segregated into even poorer prognostic groups.

Adjuvant chemotherapy. Until 1999, none of the 35 PapCa patients received any adjuvant chemotherapy. From 1999 to 2012, adjuvant gemcitabine monochemotherapy was increasingly administered in 34 of 60 (57%) patients (36% overall) and was applied more frequently in PT patients than in IT patients (48% vs 26%; $P = .032$; Table I and Table IV). Table IV shows baseline characteristics of IT and PT patients with and without adjuvant gemcitabine. In both subgroups, patients receiving chemotherapy were shown to feature more often advanced T-stages (IT: 58% vs 34%; PT: 77% vs 54%) and nodal involvement (IT: 58% vs 17%; PT: 91% vs 46%). Nodal metastases were identified as the main factor associated with gemcitabine treatment in both, IT and PT patients. With regard to the entire PapCa population, no efficacy was shown for adjuvant gemcitabine ($P = .832$; Fig 3, *A*). A substantial survival benefit, however, was demonstrated for the PT subgroup of patients receiving adjuvant gemcitabine chemotherapy compared with those PT patients who did not (32 vs 13 months; $P = .013$; Fig 3, *C*, Table IV). In contrast, an opposed tendency was found for the IT subgroup, where a trend of decreased survival became apparent in patients treated with gemcitabine monotherapy (35 vs 112 months; $P = .193$; Fig 3, *B*, Table IV).

With respect to predictive value of biomarkers, similar results were found. Patients featuring CK20-positivity (an IT tissue-marker) and treated adjuvantly with gemcitabine showed reduced survival compared with CK20-positive chemo-naïve patients (30 vs 84 months median; $P = .046$). In contrast, patients with tumors that were CK20-negative tended to live longer after adjuvant gemcitabine treatment (40 vs 23 months median; $P = .125$). CK7 and MUC2 were not able to predict chemotherapy response.

DISCUSSION

In the present study, PapCa showed great improved OS compared with PDAC (37 vs 17 months, $P < .001$), which is consistent with the published literature.[2,3] Often ascribed to the earlier occurrence of symptoms (eg, jaundice), we were able to show that this effect and the large interindividual outcome divergence of PapCa patients can be explained by the aggregation of 2

Fig 2. Survival analysis and histopathologic findings. (*A–C*): Overall survival of (*A*) all patients with ampullary carcinoma (PapCa) compared with a matching population of pancreatic cancer (PDAC) patients ($P < .001$). (*B*) PapCa patients stratified into intestinal-type (IT) and pancreaticobiliary type (PT) of cancer demonstrating diverging prognosis ($P < .001$), and (*C*) PT-PapCa compared with separately matched PDAC patients with closely resembling plots ($P = .123$). (*D–F*): Histomorphologic aspects after standard hematoxylin and eosin staining (100-fold magnification) of PDAC, PT-PapCa, and IT-PapCa. (*E*) PT-PapCa with simple or branching glands and small solid cell nests of cuboidal tumor cells featuring round, centrally located nuclei surrounded by desmoplastic stroma resembles the morphologic aspect of PDAC (*D*). In contrast, IT-PapCa (*F*) resembles duodenal or colorectal adenocarcinoma with tubular glands and columnar tumor cells with cigar-shaped basally located nuclei. (*G–I*) Prognostic relevance of immunohistochemistry markers. Overall survival of PT-PapCa patients featuring (*G*) additional CK7 expression, (*H*) lack of MUC2 expression, or (*I*) lack of CK20 compared with their IT-PapCa counterparts lacking CK7 ($P < .001$), and showing MUC2 ($P = .004$) or CK20 expression ($P = .007$), respectively. Thereby, prognostic value of hematoxylin and eosin staining (hazard ratio [HR] 2.38) might be strengthened by additional assessment of CK7 (HR 3.37) and MUC2 (HR 2.73). (*J–L*) Tissue microarray–stained sections (200-fold magnification) of (*J*) PT-PapCa with CK7 expression, and (*K*) IT-PapCa with expression of MUC2 and (*L*) CK20. *PDAC*, Pancreatic ductal adenocarcinoma.

Table I. Patients' clinical characteristics

	All PapCa, n *(%)*	*IT,* n *(%)*	*PT,* n *(%)*	P *(IT vs PT)*
No. patients	95 (100)	47 (100)	46 (100)	1.000
Demographics				
Sex, male	52 (54.7)	28 (59.6)	23 (50.0)	.408
Age, y*	65.0 [32–84]	62.0 [32–80]	67.0 [49–84]	.160
ASA score				.997
1	4 (4.2)	2 (4.3)	2 (4.3)	
2	65 (68.4)	32 (68.0)	31 (67.5)	
3	26 (27.4)	13 (27.7)	13 (28.2)	
Preoperative symptoms				
Jaundice†	68 (71.6)	32 (68.1)	36 (78.3)	.351
Abdominal pain	25 (26.3)	12 (25.5)	12 (26.1)	1.000
Weight loss‡	19 (20.0)	8 (17.0)	11 (23.9)	.450
Preoperative interventions				
ERCP	69 (72.6)	34 (72.3)	34 (73.9)	1.000
BD stenting	45 (47.4)	21 (44.7)	24 (52.2)	.825
T-stage				.022
pT1/2	45 (47.4)	28 (59.6)	16 (34.8)	
pT3/4	50 (52.6)	19 (40.4)	30 (65.2)	
Nodal involvement, pN+	45 (47.4)	13 (27.6)	31 (67.4)	<.001
Metastatic disease, M1	1 (1.1)	1 (2.1)	0	1.000
Margins involved, R1	9 (9.5)	3 (6.4)	6 (13.0)	.316
Grading				.060
Low grade, G1/G2	49 (51.6)	29 (61.7)	20 (43.5)	
High grade, G3/G4	46 (48.4)	18 (38.3)	26 (56.5)	
Operative approach				
Pylorus-preserving, PPPD	28 (29.5)	13 (27.7)	14 (30.4)	.822
D2 lymph node dissection	82 (86.3)	41 (87.2)	39 (84.8)	.773
Extended resection§	5 (5.3)	2 (4.3)	3 (6.4)	.677
Duration of operation, min*	283 [131–565]	308 [145–510]	275 [131–565]	.394
Octreotide prophylaxis	47 (49.5)	25 (53.1)	22 (47.8)	.680
Postoperative morbidity				
Total complications	48 (50.5)	25 (53.1)	21 (45.6)	.536
Nonoperative complications	13 (13.7)	7 (14.9)	6 (13.0)	1.000
Operative complications	32 (33.7)	16 (34.0)	14 (30.4)	.825
Operative revision	14 (14.7)	6 (12.8)	7 (15.2)	.773
Clavien-Dindo classification				.888
Grade I	6 (6.3)	4 (8.5)	2 (4.3)	
Grade II	13 (13.7)	6 (12.8)	5 (10.9)	
Grade III	14 (14.7)	6 (12.8)	8 (17.4)	
Grade IV	7 (7.4)	6 (12.8)	1 (2.2)	
Grade V	8 (8.4)	3 (6.4)	5 (10.9)	
Duration of stay				
ICU stay	36 (38.0)	21 (44.7)	14 (30.4)	.200
ICU duration of stay, d*	2.0 [1–101]	2.0 [1–101]	3.0 [1–40]	.583
HLOS, d*	18.0 [7–103]	17.0 [10–103]	18.0 [7–60]	.720
Adjuvant chemotherapy||	34 (35.8)	12 (25.5)	22 (47.8)	.032

*Numbers are median [range].
†Serum bilirubin >2 mg/dL (34 μmol/L).
‡Loss of >5% of body weight or absolute loss of 5 KG over the last six months, respectively.
§Resection of at least one further organ or greater parts of it.
||All patients received a gemcitabine monotherapy.
ASA, American Society of Anesthesiologists; *BD*, bile duct; *ERCP*, endoscopic retrograde cholangiopancreatography; *HLOS*, hospital duration of stay, *ICU*, intensive care unit, *IT*, intestinal type; *PapCa*, XXX; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *PT*, pancreaticobiliary type.

different tumor entities (IT and PT of PapCa) having different tumor aggressiveness, chemotherapy response, and long-term prognosis.

PT-PapCa seems to mimic the clinical course of PDAC (Fig 2, *C*). Additionally, we provide immunohistochemical evidence that PT-PapCa is

Table II. Prognostic factors: UV and MV survival analysis

	P *value*			
	UV	*MV*	*HR (MV)*	*95% CI (MV)*
General risk factors				
Sex	.819			
Age >65 y	.008	.059	1.70	0.98–2.95
ASA (>grade 2)	.495			
Surgical risk factors				
Pylorus preserving (PPPD)	.108			
Duration of operation (>300 min)	.298			
Total complications	.850			
Severe complications (CD >grade II)	.005	<.001	3.06	1.75–5.37
Oncological risk factors				
Pancreaticobiliary differentiation	<.001	.003	2.50	1.36–4.57
Advanced T-stage (pT3/4)	.202	.389	1.31	0.71–2.40
Nodal involvement (pN+)	.009	.025	2.07	1.10–3.92
High-grade	.166			
Adjuvant chemotherapy*	.832			

*All patients received gemcitabine monotherapy.
ASA, American Society of Anesthesiologists; *CD*, Clavien-Dindo; *CI*, confidence interval; *HR*, hazard ratio; *MV*, multivariate; *PPPD*, pylorus-preserving pancreaticoduodenectomy; *UV*, univariate.

Table III. Morphologic classification (H&E) and immunohistochemistry markers as predictors for overall survival

	n	P *value*	*HR*	*95% CI*
Morphologic classification (H&E)*	46	<.001	2.38	1.42–3.99
CK7+	51	.028	1.86	1.05–3.28
CK20+	29	.215	0.70	0.40–1.23
MUC2+	24	.040	0.51	0.27–0.98
CDX2+	21	.569	0.84	0.45–1.56
ß-Catenin+	11	.616	0.79	0.31–1.99
Villin+	49	.789	0.93	0.54–1.59
H&E* and CK7+	35	<.001	3.37	1.74–6.54
H&E* and MUC2−	40	.004	2.73	1.33–5.60
H&E* and CK20−	38	.007	2.32	1.22–4.40

*Pancreaticobiliary differentiation.
CI, Confidence interval; *H&E*, hematoxylin and eosin; *HR*, hazard ratio.

biologically similar to PDAC, and we hypothesize that IT-PapCa may have tumor biology like duodenal or colorectal cancer, which are characterized by a comparable immunohistochemistry profile. Hence, compared with PT-PapCa (Fig 2, *B*) and PDAC, survival of IT-PapCa was better ($P < .001$). Regarding advanced pT-stage and nodal involvement, PT-PapCa displayed more local aggressiveness in our population. Furthermore, PT tended to be classified as high-grade tumors more frequently. Nodal involvement has been identified as an independent predictor of OS by this study ($P = .025$) and others.[2,3,5,11,24-26] Nonetheless, pancreaticobiliary differentiation based on morphologic classification alone (H&E) remained the strongest oncologic risk factor for shortened OS when adjusted for advanced pT-stage and nodal involvement within multivariate analysis (HR 2.50).

Immunohistochemical characterization of PapCa has been performed previously to objectify histopathologic stratification.[2,27,28] In general, our immunohistochemical results are in line with those of Kumari et al,[29] who state that a panel of immunohistochemistry markers is primarily not helpful to classify PapCa subtypes because classification can be performed in a satisfactory manner simply on the basis of morphology. In undetermined (ie, high-grade) cases, however, it might be helpful to amend routine assessment and to determine the predominant phenotype in mixed-

Table IV. Baseline characteristics of IT and PT patients with and without adjuvant gemcitabine chemotherapy

	All IT, n *(%)*	*IT, + gemcitabine,* n *(%)*	*IT, Ø gemcitabine,* n *(%)*	*All PT,* n *(%)*	*PT, + gemcitabine,* n *(%)*	*PT, ø gemcitabine,* n *(%)*
No. patients	47 (100)	12 (26)	35 (74)	46 (100)	22 (48)	24 (52)
Sex, male	28 (60)	8 (67)	20 (57)	23 (50)	11 (50)	12 (50)
Age, y*	62.0 [32–80]	62.0 [32–80]	67.0 [49–78]	67.0 [49–84]	63.0 [32–84]	67.0 [45–81]
ASA >grade 2	13 (28)	4 (33)	9 (26)	13 (28)	6 (27)	7 (29)
Advanced T-stage (pT3/4)	19 (40)	7 (58)	12 (34)	30 (65)	17 (77)	13 (54)
Nodal involvement (pN+)	13 (28)	7 (58)	6 (17)	31 (67)	20 (91)	11 (46)
High grade (G3/G4)	18 (38)	7 (58)	11 (31)	26 (57)	12 (55)	14 (58)
Margins involved (R1)	3 (6)	1 (8)	2 (6)	6 (13)	2 (9)	4 (17)

*Numbers as median and [range].
IT, Intestinal type; *PT,* pancreaticobiliary type.

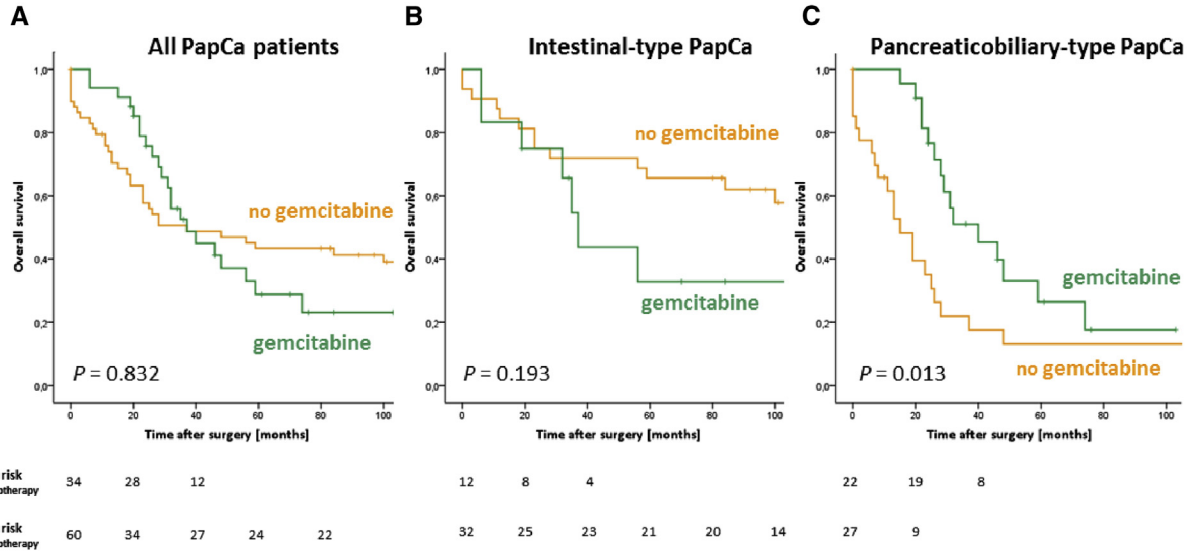


Fig 3. Survival of patients receiving or not receiving adjuvant gemcitabine. Overall survival (*A*) of all patients with PapCa ($P = .832$), (*B*) of IT-PapCa patients ($P = .193$), and (*C*) of PT-PapCa patients ($P = .013$) receiving or not receiving adjuvant gemcitabine chemotherapy, respectively. Survival benefit is shown for the PT group of patients receiving adjuvant gemcitabine compared with PT patients who did not. In major contrast, no benefit is found for IT patients. Thus, PT-PapCa not only morphologically, immunohistochemically, and clinically mimics PDAC, but should also be treated adjuvantly like it in contrast to IT-PapCa.

type tumors. CK7, CK20, and MUC2 were the most promising markers in our population. Similar to duodenal or colorectal cancer, IT-PapCa mostly express CK20 and MUC2 but lack strong and diffuse immunoreactivity for CK7. In contrast, PT-PapCa usually expresses CK7 and does not express MUC2 or CK20 just as PDAC. These findings support the idea that IT and PT tumors develop from different types of epithelia and might therefore have different biologic behavior. Indeed, in our study, expression of CK7 and lack of MUC2 were associated with decreased survival, and the prognostic value of standard histomorphologic assessment was strengthened (Table III; Fig 2, *G* and H).

Although the prognostic value of histological stratification of ampullary cancer has been demonstrated,[2,5,11] the therapeutic impact of this classification has not been worked out. Thus, need for adjuvant chemotherapy after curative resection of PapCa remains unknown. In the present study, gemcitabine has been administered more frequently in PT patients than in IT patients, which might be secondary to more advanced tumor

stages of PT-PapCa (pT3/4, pN+; Table I and Table IV). In both groups (PT and IT), however, patients receiving gemcitabine were found to have more advanced tumor stages and nodal metastases compared with chemo-naïve patients. This finding strongly suggests comparable individual indications for adjuvant treatment in both subgroups (Table IV). Efficacy of adjuvant gemcitabine could be demonstrated only for PT-PapCa patients (Fig 3, *C*). The median survival of PT patients receiving adjuvant gemcitabine was 32 months and therefore 2.5-fold greater than of those without any chemotherapy (13 months). This finding is particularly remarkable because gemcitabine was administered with a strong selection bias towards more advanced tumor stages and because statistical power was low due the small subgroup of patients. Therefore, the real efficacy of gemcitabine in PT patients might be even stronger.

In contrast, IT patients receiving adjuvant gemcitabine had no survival benefit from therapy. In fact, these patients tended to display even worse OS (35 months) compared with those IT patients not given adjuvant therapy (112 months). This contradictory effect in IT patients despite low patient numbers might be explained by a selection bias for (a noneffective) chemotherapy in a subgroup of high-risk IT-patients (pT3/4, pN+, G3/4) being individually selected for adjuvant treatment. These findings support the hypothesis of the efficacy of gemcitabine in PT-PapCa patients analogous to pancreatic cancer. Moreover, our results are consistent with data showing a lack of gemcitabine efficacy in adenocarcinomas of intestinal origin.[30] We may therefore speculate that, comparable with colorectal cancer, 5-fluororacil–based regimens may be more effective for IT-PapCa patients.

Furthermore, the present analysis may clarify results of earlier randomized controlled trials and observational studies failing to demonstrate survival benefit from adjuvant chemotherapy when PapCa was assessed as a homogenous entity.[11,31-38] Results of the European Study Group for Pancreatic Cancer-3 periampullary cancer trial initially demonstrated a lack of benefit of adjuvant chemotherapy.[39,40] On regression analysis, however, survival benefit was evident for chemotherapy after adjustment for prognostic variables. This effect may probably be biased by an underlying (but not diagnosed) pancreaticobiliary subtype that is associated with greater local tumor aggressiveness but also chemotherapy response.

The present study is limited by a number of factors, including the long treatment period and the retrospective and observational study design notably referred to chemotherapy administration being prone to selection bias. Drawing general conclusions is further restricted by the limited number of patients, especially when subgroups were analyzed. This especially applies to further substratifications into more distinct subgroups of biomarker-expression profiles as well as chemotherapy efficacy. Despite the rareness of the disease, the present study is one of the largest and most homogeneous single center studies pertaining to the population's substratification into IT and PT tumors. On the basis of the present data, randomized controlled trials will be needed considering prospective classification of IT and PT to assess chemotherapy efficacy in these different entities and to confirm our recommendation for adjuvant gemcitabine therapy in PT patients. The rarity of PapCa, however, will probably necessitate inclusion and stratification of PapCa patients within large international multicenter pancreatic and periampullary cancer trials.

We could demonstrate that IT and PT ampullary cancer are 2 distinct tumor entities with different tumor biology, local aggressiveness, chemosensitivity profiles, and diverging prognoses. Morphologic classification should remain the gold standard, but its prognostic value might be strengthened by additional immunohistochemical assessment of CK7 and MUC2 expression. PT morphologically, immunohistochemically, and clinically mimics ductal adenocarcinoma of the pancreatic head and—as a consequence—should be treated adjuvantly like pancreatic cancer. In contrast, IT morphologically and clinically mimics duodenal or colorectal cancer and might therefore be treated in accordance to those entities. Randomized controlled trials are necessary to confirm these recommendations.

We appreciate the help of Sabrina Karst, MD, for her dedicated data acquisition. We also thank Mona Melz for preparation of the TMA and Annegret Schaefer for excellent technical assistance performing the immunohistochemistry.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2015.02.001.

REFERENCES

1. Michelassi F, Erroi F, Dawson PJ, Pietrabissa A, Noda S, Handcock M, et al. Experience with 647 consecutive tumors of the duodenum, ampulla, head of the pancreas, and distal common bile duct. Ann Surg 1989;210:544-54.
2. Morini S, Perrone G, Borzomati D, Vincenzi B, Rabitti C, Righi D, et al. Carcinoma of the ampulla of Vater:

morphological and immunophenotypical classification predicts overall survival. Pancreas 2013;42:60-6.
3. Qiao QL, Zhao YG, Ye ML, Yang YM, Zhao JX, Huang YT, et al. Carcinoma of the ampulla of Vater: factors influencing long-term survival of 127 patients with resection. World J Surg 2007;31:137-43.
4. Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, et al. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. BMC Cancer 2008;8:170.
5. Westgaard A, Pomianowska E, Clausen OP, Gladhaug IP. Intestinal-type and pancreatobiliary-type adenocarcinomas: how does ampullary carcinoma differ from other periampullary malignancies? Ann Surg Oncol 2013;20:430-9.
6. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg 1998;227:821-31.
7. Bouvet M, Gamagami RA, Gilpin EA, Romeo O, Sasson A, Easter DW, et al. Factors influencing survival after resection for periampullary neoplasms. Am J Surg 2000;180:13-7.
8. O'Connell JB, Maggard MA, Manunga J Jr, Tomlinson JS, Reber HA, Ko CY, et al. Survival after resection of ampullary carcinoma: a national population-based study. Ann Surg Oncol 2008;15:1820-7.
9. Albores-Saavedra J, Schwartz AM, Batich K, Henson DE. Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program. J Surg Oncol 2009;100:598-605.
10. Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. Ann Surg Oncol 2010;17:991-7.
11. Chang DK, Jamieson NB, Johns AL, Scarlett CJ, Pajic M, Chou A, et al. Histomolecular phenotypes and outcome in adenocarcinoma of the ampulla of vater. J Clin Oncol 2013;31:1348-56.
12. Kimura W, Futakawa N, Yamagata S, Wada Y, Kuroda A, Muto T, et al. Different clinicopathologic findings in two histologic types of carcinoma of papilla of Vater. Jpn J Cancer Res 1994;85:161-6.
13. Fischer HP, Zhou H. Pathogenesis of carcinoma of the papilla of Vater. J Hepatobiliary Pancreat Surg 2004;11:301-9.
14. Howe JR, Klimstra DS, Moccia RD, Conlon KC, Brennan MF. Factors predictive of survival in ampullary carcinoma. Ann Surg 1998;228:87-94.
15. Albores-Saavedra J, Henson DE, Klimstra DS. Tumors of the gallbladder, extrahepatic bile duct, and ampulla of Vater. In: Rosai J, Sobin L, editors. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 2000. p. 259-316.
16. Roh YH, Kim YH, Lee HW, Kim SJ, Roh MS, Jeong JS, et al. The clinicopathologic and immunohistochemical characteristics of ampulla of Vater carcinoma: the intestinal type is associated with a better prognosis. Hepatogastroenterology 2007;54:1641-4.
17. Sessa F, Furlan D, Zampatti C, Carnevali I, Franzi F, Capella C. Prognostic factors for ampullary adenocarcinomas: tumor stage, tumor histology, tumor location, immunohistochemistry and microsatellite instability. Virchows Arch 2007;451:649-57.
18. Zhou H, Schaefer N, Wolff M, Fischer HP. Carcinoma of the ampulla of Vater: comparative histologic/immunohistochemical classification and follow-up. Am J Surg Pathol 2004;28:875-82.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-7.
20. Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 7th ed Oxford: Wiley Blackwell; 2009.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
22. WHO classification of tumors of the digestive system. Lyon: IARC; 2010.
23. Kononen J, Bubendorf L, Kallioniemi A, Barlund M, Schraml P, Leighton S, et al. Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med 1998;4:844-7.
24. Mizuno T, Ishizaki Y, Ogura K, Yoshimoto J, Kawasaki S. Clinical significance of immunohistochemically detectable lymph node metastasis in adenocarcinoma of the ampulla of Vater. Br J Surg 2006;93:221-5.
25. Connor S, Bosonnet L, Ghaneh P, Alexakis N, Hartley M, Campbell F, et al. Survival of patients with periampullary carcinoma is predicted by lymph node 8a but not by lymph node 16b1 status. Br J Surg 2004;91:1592-9.
26. Bettschart V, Rahman MQ, Engelken FJ, Madhavan KK, Parks RW, Garden OJ. Presentation, treatment and outcome in patients with ampullary tumours. Br J Surg 2004;91:1600-7.
27. Fischer HP, Zhou H. Pathogenesis and histomorphology of ampullary carcinomas and their precursor lesions. Review and individual findings[in German]. Pathologe 2003;24:196-203.
28. Matsubayashi H, Watanabe H, Yamaguchi T, Ajioka Y, Nishikura K, Kijima H, et al. Differences in mucus and K-ras mutation in relation to phenotypes of tumors of the papilla of vater. Cancer 1999;86:596-607.
29. Kumari N, Prabha K, Singh RK, Baitha DK, Krishnani N. Intestinal and pancreatobiliary differentiation in periampullary carcinoma: the role of immunohistochemistry. Hum Pathol 2013;44:2213-9.
30. Mani S, Kugler JW, Knost JA, Sciortino DF, Gibbons J, Garcia JC, et al. Phase II trial of 150-minute weekly infusion of gemcitabine in advanced colorectal cancer: minimal activity in colorectal cancer. Invest New Drugs 1998;16:275-8.
31. Klinkenbijl JH, Jeekel J, Sahmoud T, van PR, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776-82.
32. Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002;95:1685-95.
33. Smeenk HG, van Eijck CH, Hop WC, Erdmann J, Tran KC, Debois M, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg 2007;246:734-40.
34. Mehta VK, Fisher GA, Ford JM, Poen JC, Vierra MA, Oberhelman HA, et al. Adjuvant chemoradiotherapy for

"unfavorable" carcinoma of the ampulla of Vater: preliminary report. Arch Surg 2001;136:65-9.
35. Sikora SS, Balachandran P, Dimri K, Rastogi N, Kumar A, Saxena R, et al. Adjuvant chemo-radiotherapy in ampullary cancers. Eur J Surg Oncol 2005;31:158-63.
36. Bhatia S, Miller RC, Haddock MG, Donohue JH, Krishnan S. Adjuvant therapy for ampullary carcinomas: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys 2006;66: 514-9.
37. Krishnan S, Rana V, Evans DB, Varadhachary G, Das P, Bhatia S, et al. Role of adjuvant chemoradiation therapy in adenocarcinomas of the ampulla of vater. Int J Radiat Oncol Biol Phys 2008;70:735-43.
38. Zhou J, Hsu CC, Winter JM, Pawlik TM, Laheru D, Hughes MA, et al. Adjuvant chemoradiation versus surgery alone for adenocarcinoma of the ampulla of Vater. Radiother Oncol 2009;92:244-8.
39. Kim R, Chabot J, Saif MW. Adjuvant treatment for ampullary cancer. Highlights from the "2011 ASCO Annual Meeting." Chicago, IL, USA; June 3-7, 2011. JOP 2011;12:362-3.
40. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA 2012;308:147-56.

ORIGINAL CONTRIBUTION

Impact of Perioperative Allogeneic Red Blood Cell Transfusion on Recurrence and Overall Survival After Resection of Colorectal Liver Metastases

Tobias S. Schiergens, M.D. • Markus Rentsch, M.D. • Michael S. Kasparek, M.D.
Katharina Frenes, M.D. • Karl-Walter Jauch, M.D. • Wolfgang E. Thasler, M.D.

Department of General, Visceral, Transplantation, Vascular, and Thoracic Surgery, University of Munich, Campus Grosshadern, Munich, Germany

BACKGROUND: Perioperative allogeneic red blood cell transfusion has been conclusively shown to be associated with adverse oncologic outcomes after resection of nonmetastatic colorectal adenocarcinoma.

OBJECTIVE: The aim of the study was to identify risk factors for a perioperative transfusion and to assess the effects of transfusion on survival after curative-intended resection of hepatic metastases in patients featuring stage IV colorectal cancer.

DESIGN: This was an observational study with a retrospective analysis of a prospective data collection.

SETTING: The study was conducted at a tertiary care center.

PATIENTS: A total of 292 patients undergoing curative-intended liver resection for colorectal liver metastases were included in the study.

MAIN OUTCOME MEASURES: Univariate and multivariate analyses were performed identifying factors influencing transfusion, recurrence-free survival, and overall survival.

RESULTS: A total of 106 patients (36%) received allogeneic red blood cells. Female sex ($p = 0.00004$), preoperative anemia ($p = 0.001$), major intraoperative blood loss ($p < 0.00001$), and major postoperative complications ($p = 0.02$) were independently associated with the necessity of transfusion. Median recurrence-free and overall survival were 58 months. Allogeneic red blood cell transfusion was significantly associated with reduced recurrence-free survival (32 vs 72 months; $p = 0.008$). It was reduced further by administration of >2 units (27 months; $p = 0.02$). Overall survival was not significantly influenced by transfusion (48 vs 63 months; $p = 0.08$). When multivariately adjusted for major intraoperative blood loss and factors univariately associated, namely comorbidities, tumor load, and positive resection margins, transfusion was an independent predictor for reduced recurrence-free survival ($p = 0.03$).

LIMITATIONS: These include the retrospective and observational design, as well as the impossibility to prove causality of the association between transfusion and poor outcome.

CONCLUSIONS: In patients undergoing liver resection for colorectal liver metastases, perioperative transfusion is independently associated with earlier disease recurrence. This emphasizes appropriate blood management measures, including the conservative correction of preoperative anemia, the use of low transfusion triggers, and the minimization of intraoperative blood loss.

KEY WORDS: Allogeneic; Blood; Colorectal liver metastases; Recurrence; Survival; Transfusion.

The liver is the most common site of distant metastases of colorectal cancer, and hepatic metastases occur in approximately half of these patients.[1] Twenty percent of patients present with synchronous colorectal liver metastases (CLMs), and metachronous CLMs develop in 20% to 50%.[2,3] Liver resection for CLMs embedded in multimodality treatment strategies has been shown to be safe and oncologically effective, thereby extending survival and improving quality of life.[4,5] Despite growing experience in anatomic understanding and surgical techniques, as well as improvements in hepatic dissection devices and

Financial Disclosure: None reported.

Correspondence: Wolfgang E. Thasler, M.D., Department of General, Visceral, Transplantation, Vascular, and Thoracic Surgery, University of Munich, Campus Grosshadern, Marchioninistr 15, D-81377 Munich, Germany. E-mail: wolfgang.thasler@med.lmu.de

Dis Colon Rectum 2015; 58: 74–82
DOI: 10.1097/DCR.0000000000000233

perioperative management, major liver resections remain especially challenging procedures with risk for substantial blood loss.[6,7] In several studies and meta-analyses, perioperative allogeneic red blood cell transfusion (ABT) has been conclusively shown to be associated with adverse clinical outcomes, such as earlier recurrence and cancer-related mortality for primary tumor resection of nonmetastatic colorectal cancer.[8–12] Explanations for this adverse effect are seen in the induction of the host's immunosuppression by several mechanisms. However, up to now, there is no evidence for this effect in patients with stage IV colorectal cancer who are undergoing resection for CLM. Given the steadily extended survival of this population, analysis of the impact of perioperative transfusion may help to rank the significance of appropriate blood management measures and transfusion avoidance strategies.

The aim of this study was to identify factors that are associated with the necessity of perioperative ABT and to assess the effects of transfusion on recurrence-free survival (RFS) and overall survival (OS) after curative-intended resection of CLMs.

MATERIALS AND METHODS

Design and Study Population

From a database, prospectively collected demographic, clinical, laboratory, and perioperative data, as well as RFS and OS of patients undergoing elective, curative-intended liver resection for CLM between 2003 and 2013 at our institution, were analyzed retrospectively. The study was approved by the ethics committee of the Faculty of Medicine, Ludwig-Maximilians-University (Munich, Germany). Design, data acquisition, statistical methods, and article preparation were carried out according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13]

Data Collection

Data were collected using standardized electronic case report forms. Preoperative assessment included patient demographics (age and sex), diagnosis and specifications of tumor stage, comorbidities, underlying parenchymal liver disease, and chemotherapy. Comorbidities were assessed by patient medical history and stratified applying the ASA classification according to the ASA and Charlson comorbidity scores.[14] Preoperative anemia was defined based on the World Health Organization definition setting a threshold of 13 g/dL for male and 12 g/dL for female patients.[15] As intraoperative data, type of liver resection was recorded and stratified based on the Brisbane nomenclature.[16] Multivisceral resection was defined as resection of at least 1 additional organ or major parts of it. Duration of the operative procedure, ischemic maneuver, blood loss, and need for transfusion of red blood cell concentrates (1 unit = 300 mL) or fresh-frozen plasma were assessed. Major intraoperative blood loss was defined as the volume exceeding the population's median. ABT was performed according to current anesthesiologic and critical care guidelines (usually for hemoglobin levels <7 g/dL).[17–19] Postoperative complications were assessed according to the Clavien-Dindo classification.[20,21] Accordingly, grade 3 to 5 complications were classified as major complications.[22] In addition, specific surgical and nonsurgical complications, stay on the intensive care unit, and total length of hospital stay were documented. Thirty-day mortality was defined as death within 30 days after surgery. Survival was determined from the date of initial surgery to the date of either biopsy-proven or radiologic evidence of disease recurrence (RFS) or to the date of death or last recall (OS).

Statistical Analysis

Depending on the variable character, χ^2 test or Fisher exact test (cases of low frequency) and Kruskal-Wallis test were used where appropriate. Univariate survival analysis (RFS and OS) was performed by the Kaplan-Meier method applying the log-rank test for statistical discrimination. The number of patients at risk illustrated by Kaplan-Meier survival curves was truncated when it was less than one third of the starting figure. For continuous variables, a Cox regression model was calculated for survival. For multivariate modeling of RFS and OS, the Cox proportional hazard model was calculated for factors featuring significant univariate association and was hypothesized for adjustment. Variables that were associated with ABT were assessed as published previously.[22] Factors univariately significantly associated with ABT were subsequently entered into a multivariate logistic regression model. Results were expressed as mean ± SD or median and range. In the case of multivariate analysis of survival, the HR with its 95% CI was calculated for binary predictors. A p value <0.05 was regarded as statistically significant. For statistical analysis, SPSS statistical software package (version 20.0, IBM, Chicago, IL) and Prism (version 5.01, GraphPad, La Jolla, CA) were used.

RESULTS

Patient and Tumor Characteristics

A total of 292 patients were included in the present study, 99 women (34%) and 193 men (66%; $p = 0.01$). The median follow-up was 29 months (range, 0–119 months). Patient characteristics and oncologic data are summarized in Table 1. Median age was 65 years (range, 21–86 years). Prevalence of comorbidities and underlying parenchymal liver diseases are shown in Table 1. Ninety-one patients (31%) of the entire cohort featured a Charlson score >8, because all of the patients with International Union Against Cancer stage IV colorectal carcinoma scored at

Table 1. Patient and tumor characteristics; perioperative course

Characteristic	*All patients n (%)*	*No transfusion n (%)*	*Transfusion n (%)*	*p*
No. of patients	292 (100)	186 (63.7)	106 (36.3)	
Median age, y (range)	64.5 (21–86)	64.0 (21–86)	65.5 (32–84)	NS
Sex				0.01
Female	99 (34)	53 (28)	46 (43)	
Male	193 (66)	133 (72)	60 (57)	
Preoperative anemia[a]	106 (36)	51 (27)	55 (52)	0.0002
Comorbidities				
ASA >2	191 (65)	125 (67)	66 (62)	NS
Charlson score >8	91 (31)	58 (31)	33 (31)	NS
Cardiovascular disease	47 (16)	34 (18)	13 (12)	NS
Arterial hypertension	64 (22)	44 (24)	20 (19)	NS
Chronic lung disease	14 (5)	8 (4)	6 (6)	NS
Diabetes mellitus	36 (12)	26 (14)	10 (10)	NS
BMI >30 kg/m^2	49 (17)	32 (17)	17 (16)	NS
Hepatic preconditions				
Steatosis	174 (60)	107 (58)	67 (63)	NS
Fibrosis	44 (15)	22 (12)	22 (21)	NS
Cirrhosis	2 (1)	2 (1)	0	NS
Serum-bilirubin elevated[b]	20 (7)	12 (6)	8 (8)	NS
Serum-cholinesterase activity, kU/L	7.6 ± 1.8	7.6 ± 1.7	7.3 ± 1.9	NS
Primary tumor				NS
Colon	151 (52)	97 (52)	53 (50)	
Rectum	141 (48)	89 (48)	53 (50)	
Primary tumor stage				
pT3/pT4	211 (72)	133 (72)	78 (74)	NS
pN+	154 (53)	100 (54)	54 (51)	NS
Tumor markers				
CEA elevated[c]	159 (54)	108 (58)	51 (48)	NS
CA 19-9 elevated[d]	84 (29)	51 (27)	33 (31)	NS
Timing of development				NS
Synchronous[e]	100 (34)	59 (32)	41 (39)	
Metachronous	192 (66)	127 (68)	65 (61)	
More than 3 hepatic metastases	43 (15)	19 (10)	24 (22)	0.006
Maximum metastasis diameter >50 mm	52 (18)	28 (15)	24 (23)	NS
Presence of another malignancy	24 (8)	12 (6)	12 (11)	NS
Concomitant extrahepatic colorectal cancer metastases	34 (12)	19 (10)	15 (14)	NS
Preoperative chemotherapy	207 (71)	129 (69)	78 (74)	NS
Extent of liver resection				0.04
Major hepatectomy	92 (32)	50 (27)	41 (39)	
Right hepatectomy	45 (15)	25 (13)	20 (19)	
Left hepatectomy	38 (13)	21 (11)	17 (16)	
Extended right hepatectomy	9 (3)	5 (3)	4 (4)	
Minor hepatectomy	200 (68)	136 (73)	65 (61)	
Wedge/atypical	115 (39)	75 (40)	40 (38)	
Segmentectomy	33 (11)	23 (12)	10 (10)	
Left lateral sectionectomy (segments II and III)	18 (6)	14 (8)	4 (4)	
Right posterior sectionectomy (segments VI and VII)	18 (6)	12 (6)	6 (6)	
Other bisegmentectomy	16 (5)	10 (5)	6 (6)	
Laparoscopic resection	25 (9)	15 (8)	10 (9)	NS
Resected liver volume, mL	342 ± 338	309 ± 318	397 ± 366	NS
Extended resection	67 (23)	34 (18)	32 (30)	0.01
Ischemic maneuver	69 (24)	45 (24)	24 (23)	NS
Duration of ischemic maneuver, min	4.2 ± 10.5	4.3 ± 10.7	3.9 ± 10.1	NS
Duration of resection, min	189.0 ± 74.1	168.0 ± 56.1	225.0 ± 86.1	0.0003
Blood loss, mL	943 ± 1686	441 ± 407	1863 ± 2545	0.0008
Blood loss >1000 mL	89 (30)	24 (13)	65 (61)	<0.00001
No. of perioperative RBCs	1.01 ± 2.50		2.74 ± 2.50	
No. of intraoperative RBCs	1.05 ± 2.50		2.89 ± 3.40	
No. of postoperative RBCs	0.52 ± 2.80		1.42 ± 4.60	

(*Continued*)

Table 1. *Continued*

Characteristic	All patients n (%)	No transfusion n (%)	Transfusion n (%)	p
Intraoperative FFPs	23 (8)	0	23 (22)	0.0003
No. of intraoperative FFPs	0.62 ± 2.80	0	1.70 ± 4.50	0.0006
Total complications	116 (40)	64 (34)	52 (49)	0.02
Major complications	77 (26)	38 (20)	40 (38)	0.002
Surgical complications	79 (27)	40 (22)	39 (37)	0.006
Nonsurgical complications	57 (20)	31 (17)	26 (25)	NS
Total hospital length of stay	15.0 ± 13.4	13.2 ± 13.9	18.4 ± 11.9	0.001
ICU	119 (41)	57 (31)	62 (58)	0.0003
ICU length of stay	2.3 ± 7.2	1.3 ± 5.0	3.9 ± 9.7	0.0005
30-day mortality	14 (5)	8 (4)	6 (6)	NS
Resection margins involved				
R1	8 (3)	5 (3)	3 (3)	NS
R2	4 (1)	2 (1)	2 (2)	NS
Postoperative chemotherapy	168 (58)	108 (58)	60 (57)	NS
Recurrence	106 (36)	61 (33)	45 (42)	NS
Hepatic	89 (30)	51 (27)	38 (36)	
Extrahepatic nonlocal	21 (7)	11 (6)	10 (9)	
Local	13 (4)	9 (5)	4 (4)	

CA 19-9 = cancer antigen 19-9; FFP = fresh-frozen plasma; ICU = intensive care unit; NS = not significant; RBC = red blood cell concentrate.
[a]Hemoglobin level was <13 g/dL for men and <12 g/dL for women.
[b]Serum bilirubin level was >2 mg/dL (34 μmol/L).
[c]Serum CEA level was >3.4 ng/mL.
[d]Serum CA 19-9 level was >37.0 U/mL.
[e]Metastases were assessed before or within 3 months after primary tumor resection.

least 8 points. More than two thirds of all patients (72%) had advanced pT stages (pT3/pT4), and approximately half (53%) showed nodal involvement (pN+) of the primary tumor. The location of the primary tumor site was balanced (colon, 52%; rectum, 48%). One third of all patients (34%) featured synchronous metastases, whereas metachronous hepatic metastatic disease developed in the other two thirds. Thirty-four patients (12%) had concomitant extrahepatic metastases. The majority of patients (71%) received preoperative chemotherapy; 15% of those including antibodies (bevacizumab or cetuximab).

Perioperative Course

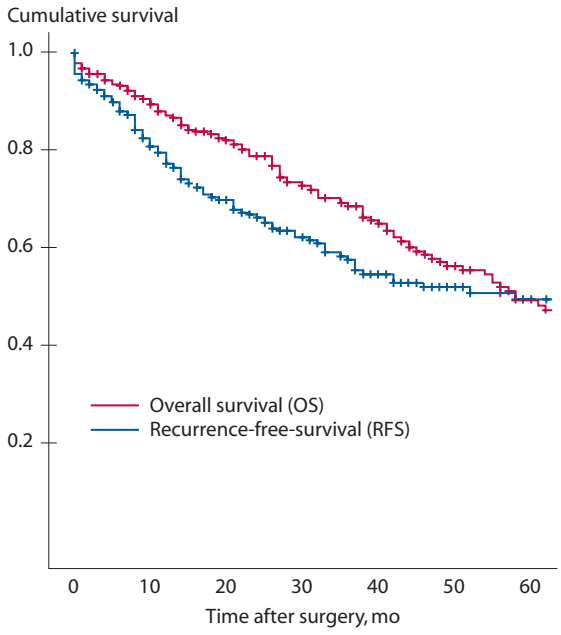
Ninety-two patients (32%) underwent major liver resection (Table 1). Twenty-nine patients (10%) underwent simultaneous resection of the primary tumor and the metastatic liver disease, and 19 of those were wedge resections. Twenty-five patients (9%) underwent laparoscopic resection. Complications occurred in 116 patients (40%), with 77 patients (26%) experiencing major complications. The 30-day mortality rate was 5% for the entire cohort. The mean total length of hospital stay was 15 ± 13 days. All of the perioperative data are reported in Table 1.

Allogeneic Red Blood Cell Transfusion

A total of 106 patients (36%) received perioperative ABT, with 48 patients (16%) receiving >2 units. All of the patients undergoing ABT were transfused intraoperatively, with 21 patients (7%) receiving additional ABT during the postoperative course. There was no preoperative allogeneic blood administration. The mean number of perioperative red blood cell concentrates was 1.0 ± 2.5 units. ABT was univariately associated with female sex, preoperative anemia, more than 3 hepatic metastases, and major or extended liver resection (Table 1). It was also related to associated operative risk factors, along with major intraoperative blood loss (as a continuous variable or more than the median), the incidence of postoperative complications, both major and surgical complications, postoperative treatment on the intensive care unit, and the length of intensive care unit and total hospital stay (Table 1). Simultaneous colorectal resection tended to be associated with a higher rate of ABT ($p = 0.19$). By multivariate logistic regression, female sex ($p = 0.00004$), preoperative anemia ($p = 0.001$), major intraoperative blood loss ($p < 0.00001$), and major postoperative complications ($p = 0.02$) were the only independent predictors of perioperative transfusion.

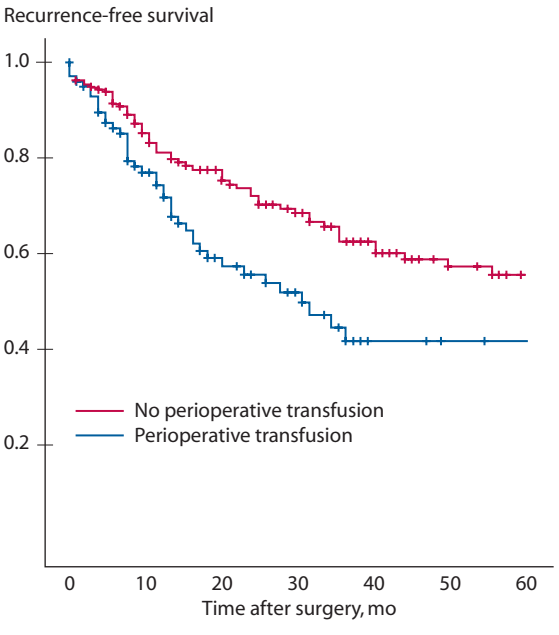
Analysis of Survival

By the end of the study, 112 patients (38%) had died. Tumor recurrence occurred in 106 patients (36%), 89 (84%) were hepatic recrudescence (Table 1). For the entire population, both median RFS and OS were 58 months (Fig. 1). At this point, RFS and OS Kaplan-Meier estimators crossed and the RFS estimator fell below OS (Fig. 1). Median RFS of those receiving ABT was significantly shorter compared with those without ABT (32 vs 72 months; $p = 0.009$; Fig. 2). In addition, the frequency of recurrence tended to be higher in transfused patients (42% vs 33%; $p = 0.06$; Table 1). When stratified by the number of red blood cell concentrate units



Patients at risk (OS)	292	177	101	49
Patients at risk (RFS)	292	137	64	35

Figure 1. Overall survival and recurrence-free survival of the entire cohort were 58 months. At this time point, the Kaplan-Meier estimators cross, indicating patients on average dying of causes other than colorectal cancer disease recurrence.



Patients at risk (No ABT)	186	100	53	30
Patients at risk (ABT)	106	36	10	

Figure 2. Recurrence-free survival stratified by perioperative transfusion. Median time to first recurrence was 32 months for those receiving red blood cell concentrates and 72 months without allogeneic red blood cell transfusion (ABT; $p = 0.008$).

transfused (Fig. 3), the RFS of patients receiving >2 units was shown to be further reduced (27 months) compared with those receiving 1 to 2 units (37 months; Fig. 3). Median OS of patients receiving ABT (48 months) was also lower compared with patients who were not transfused (63 months); however, this was not statistically significant ($p = 0.09$). OS only moderately declined with more transfusions administered: the median OS of those receiving >2 units was 40 months, which was not significantly different from that of patients receiving 1 to 2 units (48 months).

Results of univariate analysis for RFS and OS are shown in Table 2. Hepatic tumor load (18 vs 73 months; $p = 0.00006$), a Charlson score >8 (33 vs 72 months; $p = 0.04$), ABT (see above), and positive resection margins (14 vs 70 months; $p = 0.008$) significantly reduced RFS. Multivariate analyses of RFS and OS are shown in Table 3. Independent predictors for RFS were the presence of more than 3 metastases ($p = 0.005$; HR 2.19; 95% CI 1.27–3.76), perioperative ABT ($p = 0.03$; HR 1.65; 95% CI 1.05–2.61), and positive resection margins ($p = 0.02$; HR 2.21; 95% CI 1.13–4.33). Notably, ABT was a significant predictor of RFS independent of blood loss and other associated oncologic variables, including tumor load and positive margins. OS was independently predicted by age >70 years ($p = 0.02$; HR 1.64; 95% CI 1.10–2.50), a Charlson score >8 ($p = 0.03$; HR 1.53; 95% CI 1.05–2.25), and major hepatic resections ($p = 0.01$; HR 1.63; 95% CI 1.11–2.40).

DISCUSSION

The purpose of this study was to identify factors associated with the necessity for allogeneic blood transfusion during resection of CLMs and to evaluate the effect of transfusion on RFS and OS. Our data show female sex, preoperative anemia, major intraoperative blood loss, and major postoperative complications as independently demanding transfusion. The present study further demonstrates that perioperative allogeneic blood transfusion is associated with earlier disease recurrence independent of blood loss, comorbidities, and associated oncologic risk factors, such as tumor load and positive resection margins. In addition, larger quantities of transfusion seem to have an even greater impact, further shortening RFS.

The first report of a follow-up after ABT by Burrows and Tartter[10] reported an earlier recurrence of primary colorectal cancer. It was followed by several studies including high-quality meta-analyses conclusively underlining this effect in nonmetastatic colorectal cancer and other cancer types.[8–12,22] Previously, Acheson and colleagues[8] conducted a large meta-analysis of the effect of ABT on the outcome of patients undergoing surgery for nonmetastatic colorectal cancer, assessing 20,795 patients with 108,838 patient-years. They found ABT to be associated with increased all-cause and cancer-related mortality, as well as combined recurrence-metastasis-death. The con-

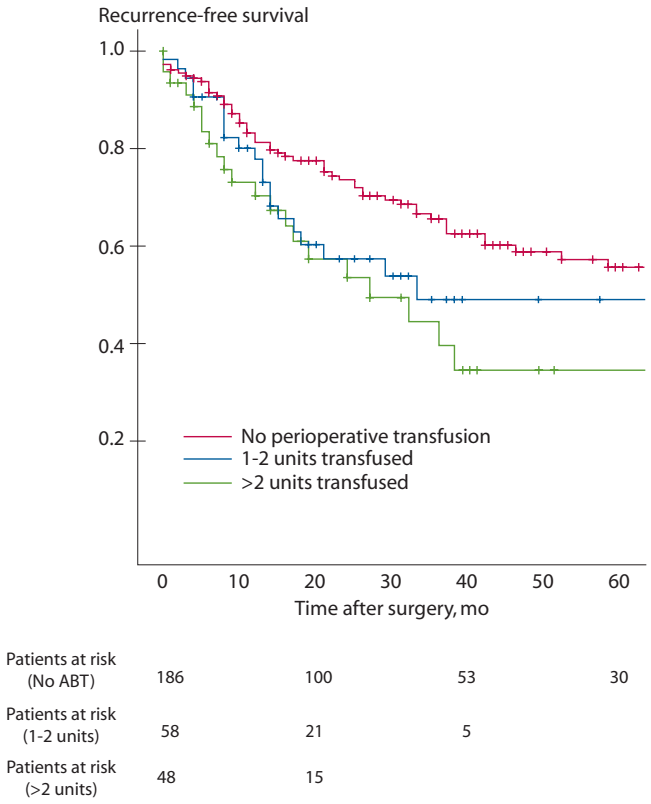


Figure 3. Recurrence-free survival receiving red blood cell concentrates or not stratified by number of units transfused. Median recurrence-free survival without allogeneic red blood cell transfusion (ABT) was 72 months; for those receiving 1 to 2 units, 37 months; and for those receiving >2 units, 27 months ($p = 0.005$).

clusion of this study extracting data from 55 publications was that ABT is associated with adverse clinical outcomes.[8]

The mechanism by which ABT increases the risk for tumor recurrence is not fully understood. ABT is thought to bear the risk to induce a status of relative immunosuppression in the host by a decrease of natural killer cell activity, phagocytic activity, an increase in suppressor T-cell activity with inhibition of interleukin 2, and sFAS ligand and sHLA molecule transfusion.[22–27] It has been hypothesized that disseminated tumor cells in patients undergoing potentially curative resections might escape immunologic surveillance and thereby disseminate predisposing the individual to an earlier recurrence.[22] Transfusion-acquired immunomodulation after oncologic resection has been attributed as a potential risk factor for earlier recurrence best described for colorectal and hepatocellular carcinomas, as well as carcinoma of the pancreas.[8,28,29]

To our knowledge, there are no data available assessing this effect after resection of CLMs in patients with stage IV colorectal cancer. However, during the past 20 years, resection of CLMs embedded in multimodality treatment strategies has been increasingly accepted and shown to be safe and of oncologic benefit.[4,5,30,31] This is underlined by the excellent median RFS and OS of our population (58 months). Furthermore, in our population, from the time point of 58 months after surgery, patients on average died of causes other than colorectal cancer recurrence (Fig. 1). From the oncologic point of view, this emphasizes not only the highly effective (multimodal) therapy but also the significance of identifying factors that influence RFS in this postoperative period. Given this fact and the strong evidence for transfusion being associated with poorer outcomes in nonmetastatic colorectal cancer, assessing the impact of transfusion in patients undergoing resection of CLMs should be of major interest.

Our results strongly support the theory of an adverse effect of ABT and corroborate the findings of the investigations cited above for this patient population. We demonstrate that RFS is significantly shortened after transfusion and that ABT is an independent predictor of decreased RFS when adjusted for confounders such as blood loss, comorbidities, and associated oncologic risk factors, including

Table 2. Univariate analysis of recurrence-free and overall survival

Risk factors	*Recurrence-free survival p*	*Overall survival p*
Age >70 y	0.89	0.005
Sex	0.22	0.77
Primary tumor	0.24	0.16
Timing of development	0.13	0.53
More than 3 hepatic metastases	0.00006	0.04
Maximum metastasis diameter >50 mm	0.42	0.04
Primary tumor stage		
pT3/pT4	0.98	0.64
pN+	0.41	0.70
Concomitant extrahepatic colorectal cancer metastases	0.44	0.03
Preoperative chemotherapy	0.42	0.26
Tumor markers		
CEA elevated	0.92	0.97
CA 19-9 elevated	0.49	0.66
Comorbidities		
Charlson score >8	0.04	0.006
ASA >2	0.89	0.23
Perioperative parameters		
Major hepatectomy	0.43	0.003
Blood loss >1000 mL	0.19	0.67
Perioperative ABT	0.008	0.09
Transfusion of >2 units RBCs	0.02	0.05
Perioperative FFP transfusion	0.74	0.48
Morbidity		
Total complications	0.10	0.007
ICU	0.18	0.02
Surgical complications	0.13	0.02
Nonsurgical complications	0.58	0.03
Operative revision	0.77	0.0003
Pathologic results		
Resection margins involved (R1/2)	0.008	0.0003
Steatosis/fibrosis	0.92	0.63
Postoperative chemotherapy	0.001	0.51

ABT = allogeneic red blood cell transfusion; CA 19-9 = cancer antigen 19-9; FFP = fresh-frozen plasma; ICU = intensive care; RBC = red blood cell concentrate;

Table 3. Multivariate analysis of recurrence-free and overall survival

	Recurrence-free survival			
Risk factors	*p*	*HR*	*95% CI*	*Forest plot*
Charlson score >8	0.09	1.42	0.94–2.15	
More than 3 hepatic metastases	0.005	2.19	1.27–3.76	
ABT	0.03	1.65	1.10–2.61	
Major blood loss	0.74	1.09	0.67–1.75	
R1/2	0.02	2.21	1.13–4.33	
	Overall survival			
	p	*HR*	*95% CI*	*Forest plot*
Age >70 y	0.02	1.64	1.10–2.50	
Charlson score >8	0.03	1.53	1.05–2.25	
Complications	0.03	1.51	1.03–2.20	
Major resection	0.01	1.63	1.11–2.40	

ABT = allogeneic red blood cell transfusion.

tumor load and positive resection margins. Our results suggest a dose-dependent effect of ABT with >2 units having an even more pronounced effect on RFS, which is in line with another report evaluating the effect in pancreatic cancer.[22] Although not being associated with RFS, we identified female sex, preoperative anemia, major intraoperative blood loss, and major postoperative complications as independent risk factors for the necessity of perioperative ABT. This supports other findings demonstrating preoperative anemia being independently associated with ABT and being a promising therapeutic target to avoid perioperative transfusion.[8,22] Kneuertz and colleagues found that red blood cell concentrates, when transfused postoperatively, exhibited a greater negative impact on survival than intraoperatively transfused blood; however, this was discussed as an effect of a markedly higher number of units transfused after the resection than administered intraoperatively, thereby biasing this finding.[22] In our study, most ABTs have been administered intraoperatively, resulting in an opposite effect. We therefore believe, matching the theory mentioned above, that ABT, when administered in temporal proximity to the surgical procedure, bears the risk of reduced RFS and OS. Other investigations, however, showed ABT not being associated with worse outcomes after oncologic resection including colorectal surgery,[9,32,33] and, thus, the presumption of an adverse effect of ABT remains controversial.

One key issue is whether the association between ABT and the outcome variables analyzed represent a causative effect or whether there are unmanageable confounders acting inwardly. The subpopulation of transfused patients may represent a compromised and vulnerable cohort, and poor outcomes may be attributed to other factors associated with ABT unless accounted for in a multivariate model. The present study, however, included a multitude of prospectively assessed demographic, medical, oncologic, and perioperative key factors and their impact on ABT, RFS, and OS, thereby enabling multivariate calculations with high statistical power by inclusion of a large subset of patients. This enabled us to adequately adjust for confounding variables. In fact, all of the factors influencing RFS were adjusted by application of the Cox multivariate survival model demonstrating ABT significantly shortening RFS adjusted for blood loss, comorbidities, and associated oncologic risk factors as tumor load and positive resection margins that could have been hypothesized to be responsible for a poor outcome in transfused patients. The hazardous effect of transfusion is further underlined by the fact that major surgery (ie, hemihepatectomies) and greater blood loss did not increase the risk for earlier disease recurrence as transfusion of allogeneic blood itself did.

Given the retrospective and observational nature of this analysis, it is difficult to assess whether ABT could have been prevented. We believe, however, that patients may benefit from avoiding ABT. This has to be thoroughly taken into account when multivisceral approaches (ie, simultaneous resections) are considered. However, we believe, that established oncologic concepts such as the (even extended) resection of CLM should not be questioned. Our results attract notice to blood management measures, including correction of preoperative anemia by administration of iron, recombinant human erythropoietin, folic acid, and vitamin B_{12} to avoid ABT.[8,34–38] Preoperative correction of anemia by those measures could be an auspicious approach for future randomized trials. The application of low transfusion triggers where appropriate may be another approach. Our results further emphasize the oncologic significance of a reduction of intraoperative blood loss by blood saving techniques, such as autologous cell-salvage devices, hemodilution, and adherence to a low central venous pressure (≤6 mm Hg). Ischemic maneuvers

(temporary hepatic vascular inflow occlusion) were not associated with morbidity or OS in a recently published study.[39] A more liberal application in selected patients might be another option to avoid blood loss.

CONCLUSION

In patients undergoing liver resection for CLMs, perioperative allogeneic blood transfusion is independently associated with earlier disease recurrence, with larger quantities of transfusion having an even greater impact. This emphasizes appropriate blood management measures, including the conservative correction of preoperative anemia, the use of low transfusion triggers, and the minimization of intraoperative blood loss.

ACKNOWLEDGMENTS

The authors thank Stephanie Schreiber, Dr Carsta Stielow, and Dr Hans-Martin Hornung for their dedicated work with the patient data collection and information technology administration of the database.

REFERENCES

1. Cooper GS, Yuan Z, Landefeld CS, Johanson JF, Rimm AA. A national population-based study of incidence of colorectal cancer and age: implications for screening in older Americans. *Cancer*. 1995;75:775–781.
2. de Liguori Carino N, van Leeuwen BL, Ghaneh P, Wu A, Audisio RA, Poston GJ. Liver resection for colorectal liver metastases in older patients. *Crit Rev Oncol Hematol*. 2008;67:273–278.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
4. Brown RE, Bower MR, Martin RC. Hepatic resection for colorectal liver metastases. *Surg Clin North Am*. 2010;90:839–852.
5. Quan D, Gallinger S, Nhan C, et al.; Surgical Oncology Program at Cancer Care Ontario. The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: a systematic review. *Surgery*. 2012;151:860–870.
6. Gomez D, Morris-Stiff G, Wyatt J, Toogood GJ, Lodge JP, Prasad KR. Surgical technique and systemic inflammation influences long-term disease-free survival following hepatic resection for colorectal metastasis. *J Surg Oncol*. 2008;98:371–376.
7. Vauthey JN, Pawlik TM, Abdalla EK, et al. Is extended hepatectomy for hepatobiliary malignancy justified? *Ann Surg*. 2004;239:722–730.
8. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. *Ann Surg*. 2012;256:235–244.
9. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev*. 2006;(1):CD005033.
10. Burrows L, Tartter P. Effect of blood transfusions on colonic malignancy recurrent rate. *Lancet*. 1982;2:662.
11. Chung M, Steinmetz OK, Gordon PH. Perioperative blood transfusion and outcome after resection for colorectal carcinoma. *Br J Surg*. 1993;80:427–432.
12. Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. *Transfusion*. 1995;35:760–768.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
15. Jans Ø, Jørgensen C, Kehlet H, Johansson PI; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. *Transfusion*. 2014;54:717–726.
16. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12:351–355.
17. Hardy JF. Current status of transfusion triggers for red blood cell concentrates. *Transfus Apher Sci*. 2004;31:55–66.
18. Carson JL, Ferreira G. Transfusion triggers: how low can we go? *Vox Sang*. 2004;87(suppl 2):218–221.
19. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care: Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409–417.
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
21. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250:187–196.
22. Kneuertz PJ, Patel SH, Chu CK, et al. Effects of perioperative red blood cell transfusion on disease recurrence and survival after pancreaticoduodenectomy for ductal adenocarcinoma. *Ann Surg Oncol*. 2011;18:1327–1334.
23. Kaplan J, Sarnaik S, Gitlin J, Lusher J. Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. *Blood*. 1984;64:308–310.
24. Waymack JP, Gallon L, Barcelli U, Trocki O, Alexander JW. Effect of blood transfusions on immune function: III–alterations in macrophage arachidonic acid metabolism. *Arch Surg*. 1987;122:56–60.
25. Innerhofer P, Tilz G, Fuchs D, et al. Immunologic changes after transfusion of autologous or allogeneic buffy coat-poor versus WBC-reduced blood transfusions in patients undergoing arthroplasty: II–activation of T cells, macrophages, and cell-mediated lympholysis. *Transfusion*. 2000;40:821–827.
26. Ghio M, Contini P, Mazzei C, et al. Soluble HLA class I, HLA class II, and Fas ligand in blood components: a possible key to explain the immunomodulatory effects of allogeneic blood transfusions. *Blood*. 1999;93:1770–1777.
27. Blajchman MA. Immunomodulation and blood transfusion. *Am J Ther*. 2002;9:389–395.

28. Dionigi G, Rovera F, Boni L, et al. The impact of perioperative blood transfusion on clinical outcomes in colorectal surgery. *Surg Oncol.* 2007;16(suppl 1):S177–S182.
29. Kwon AH, Matsui Y, Kamiyama Y. Perioperative blood transfusion in hepatocellular carcinomas: influence of immunologic profile and recurrence free survival. *Cancer.* 2001;91:771–778.
30. Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver Int.* 2009;29:89–102.
31. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol.* 2007;25:4575–4580.
32. Müller SA, Mehrabi A, Rahbari NN, et al. Allogeneic blood transfusion does not affect outcome after curative resection for advanced cholangiocarcinoma. *Ann Surg Oncol.* 2014;21:155–164.
33. Busch OR, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. *N Engl J Med.* 1993;328:1372–1376.
34. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol.* 2004;22:1301–1307.
35. Theusinger OM, Leyvraz PF, Schanz U, Seifert B, Spahn DR. Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: efficacy and limits–a prospective study. *Anesthesiology.* 2007;107:923–927.
36. Okuyama M, Ikeda K, Shibata T, Tsukahara Y, Kitada M, Shimano T. Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. *Surg Today.* 2005;35:36–40.
37. Weber RS, Jabbour N, Martin RC 2nd. Anemia and transfusions in patients undergoing surgery for cancer. *Ann Surg Oncol.* 2008;15:34–45.
38. Spahn DR, Moch H, Hofmann A, Isbister JP. Patient blood management: the pragmatic solution for the problems with blood transfusions. *Anesthesiology.* 2008;109:951–953.
39. Schiergens TS, Stielow C, Schreiber S, et al. Liver resection in the elderly: significance of comorbidities and blood loss. *J Gastrointest Surg.* 2014;18:1161–1170.

J Gastrointest Surg (2014) 18:1161–1170
DOI 10.1007/s11605-014-2516-2

ORIGINAL ARTICLE

Liver Resection in the Elderly: Significance of Comorbidities and Blood Loss

Tobias S. Schiergens · Carsta Stielow · Stefanie Schreiber · Cyrill Hornuss · Karl-Walter Jauch · Markus Rentsch · Wolfgang E. Thasler

Received: 9 January 2014 / Accepted: 25 March 2014 / Published online: 9 April 2014

Abstract
Objective Liver resection is increasingly performed in elderly patients who are suspected of increased postoperative morbidity (PM) and reduced overall survival (OS). Patient selection based on the identification of age-adjusted risk factors may help to decrease PM and OS.
Design and Participants Prospectively collected data of 879 patients undergoing elective hepatic resection were analyzed. This population was stratified into three age cohorts: >70 years (n=228; 26 %), 60–69 years (n=309; 35 %), and <60 years (n=342; 39 %). Multivariate survival analysis was performed.
Results The incidence of severe (p<0.01) and non-surgical (p<0.001) postoperative complications was higher in older compared to younger patients. Major estimated blood loss (EBL; p=0.039) and comorbidities (p=0.002) independently increased PM. EBL was comparable between all age cohorts. However, preexisting comorbidities, major EBL, and postoperative complications markedly decreased OS in contrast to younger patients. Adjusted for age, independent predictors of OS were comorbidities (HR=1.51; p=0.001), major hepatectomy (HR=1.33; p=0.025), increased EBL (HR=1.32; p=0.031), and postoperative complications (HR=1.64; p<0.001).
Conclusion Although increased age should not be a contraindication for liver resection, this study accents the avoidance of major blood loss in elderly patients and a stringent patient selection based on preexisting comorbidities.

Keywords Liver resection · Hepatectomy · Elderly · Outcome · Risk factors

Introduction

The global trend of an increasing life expectancy and average health status results in a widening of indications for liver surgery in a geriatric population.[1] Thus, the number of elderly patients scheduled for hepatobiliary surgery, particularly hepatic resection, has dramatically increased worldwide.[1–3] For the USA, Smith et al. reported an expected increase of 67 % in cancer incidence among patients 65 years and older from 2010 to 2030 compared to 11 % among younger patients.[1,4] Despite improved perioperative care, surgery in aged patients is expected to feature higher risks of restricted outcomes due to an age-associated decline in liver function and increased perioperative morbidity as a result of a higher incidence of associated medical conditions as coronary artery disease or diabetes. Altogether, high age is still regarded as an adverse factor for liver resection.[5,6]

Several studies with mainly retrospective design and small patient numbers have investigated the outcome of elderly patients after liver resection.[1,2,5,7–18] There is some evidence that especially minor resections can be performed safely and that the outcome of major resections depends on future liver remnant volume and the quality of liver parenchyma. Increasing age seems to be associated with a higher postoperative mortality notably after major hepatic resection.[1,2] Age-specific variables increasing the perioperative risk of elderly

T. S. Schiergens · C. Stielow · S. Schreiber · K.-W. Jauch · M. Rentsch · W. E. Thasler (✉)
Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, University of Munich, Campus Grosshadern, Marchioninistr. 15, 81377 Munich, Germany
e-mail: Wolfgang.Thasler@med.uni-muenchen.de

C. Hornuss
Department of Anesthesiology, University of Munich, Munich, Germany

patients—notably those being influenceable—however, have not been precisely worked out for this specific age group.

The objective of this study was to compare perioperative characteristics, postoperative morbidity (PM), and overall survival (OS) of three age cohorts undergoing liver resection in a European high-volume single center and to assess age-adjusted predictors of PM and OS.

Patients and Methods

Design and Study Population

Demographic and perioperative data as well as the (long-term) survival of patients who underwent elective hepatic resection between 2003 and 2012 at the University of Munich Hospital, Campus Grosshadern were prospectively collected using standardized electronic case report forms. For age stratification according to studies previously published,[5,7,12,16,19] *elderly patients* (EP) were defined as those with an age of 70 years and older. Patients with the age of 60–69 years were defined as *young-olds* (YO), and those with the age of below 60 years as *young patients* (YP). The study was approved by the Ethics Committee, Faculty of Medicine, Ludwig-Maximilians-University (LMU). Design, data acquisition, statistical methods, and manuscript preparation were carried out according to STROBE guidelines for the strengthening of the reporting of observational studies.[20]

Data Collection

Preoperative assessment included patient demographics (age, gender), diagnosis, and specifications of tumor type, tumor stage, comorbidities, underlying parenchymal liver disease confirmed by histopathology, and preoperative chemotherapy. Comorbidities were stratified applying the ASA classification according to the American Association of Anesthesiologists as well as the Charlson comorbidity index (CCI).[21] As intraoperative data, the type of liver resection was classified based upon the Brisbane nomenclature.[22] Furthermore, the duration of the operative procedure, estimated intraoperative blood loss (EBL), and perioperative transfusion of allogeneic red blood cells (ABT) or fresh frozen plasma (FFP) were assessed. ABT was performed according to anesthesiological guidelines.[23] Multivisceral resection was defined as the resection of at least one further organ. Postoperative complications were assessed according to the validated Clavien-Dindo classification.[24,25] Specific surgical and non-surgical complications, ICU stay, and the total length of hospital stay were documented. Hepatic dysfunction and liver failure were defined according to Menon et al.[10] Criteria for postoperative morbidity were assessed according to Reddy et al.[1] with modifications as follows: Incidence of postoperative complications grade III and higher according to Clavien-Dindo or complications as cholangitis, bile leak, bacteremia and sepsis, deep vein thrombosis, pulmonary embolism, myocardial infarction, arrhythmia, and pneumonia that did not meet the criteria of grade III complications or higher. Thirty-day mortality was defined as death within 30 days after surgery. OS was determined from the date of initial surgery to the date of death or last recall. R2-resected patients were excluded from survival analysis.

Statistical Analysis

Dependent on the variable's character, chi-square test, Fisher's exact test, or Kruskal-Wallis test were utilized where appropriate. Univariate survival analysis was performed by the Kaplan-Meier method applying the log-rank test for the statistical discrimination of binary variables. For continuous variables, a Cox regression model was calculated for OS. For multivariate survival analysis, Cox's proportional hazard model was applied. Using logistic regression models, univariate and multivariate analyses of PM were carried out. Results were expressed as mean values±standard deviation (SD) or median and range (minimum and maximum). In case of multivariate analysis for PM or OS, odds ratio (OR) or hazard ratio (HR) with their 95 % confidence intervals (95 % CI) were calculated for binary risk factors. Concerning significance levels, $p<0.05$ was regarded as statistically significant and $p<0.001$ as highly significant. For statistical analysis, SPSS software (version 20.0, IBM, Chicago, Ill) and Prism (version 3.0, GraphPad, La Jolla, CA) were used.

Results

Study Population and Follow-up

Eight hundred seventy-nine patients were included in the present study. Of these, 228 were older than 70 years (EP, 26 %), 309 were 60–69 years (YO, 35 %), and 342 were younger than 60 years (YP, 39 %). Median follow-up was 24 (0–119) months. Of all patients, 329 (37 %) had deceased by the end of the study.

Comparative Analysis of Age Cohorts

Comparisons of the three age cohorts are shown in Tables 1 and 2. Gender distribution was significantly different in the three groups with a rising male fraction in the elderly cohorts. Overall, 95 patients (11 %) had a benign diagnosis whereat 66 of these were younger than 60 years. The frequency of primary malignant liver tumors and liver metastases did not differ between the three age cohorts. Hepatocellular carcinoma (HCC) followed by cholangiocarcinoma (CCC) were the leading primary hepatic malignancies in all patients. Most

Table 1 Patients' and tumor characteristics

	All patients n=879 (%)	Age <60 years (YP) n=342 (%)	Age 60–69 years (YO) n=309 (%)	Age ≥70 years (EP) n=228 (%)	p value
Age	60.6±13.3	47.3±10.4	65.0±2.7	74.7±2.7	<0.001
Gender					
Female	392 (45)	180 (53)	129 (42)	83 (36)	<0.001
Male	487 (55)	162 (47)	180 (58)	145 (64)	
Diagnosis					
Benign	95 (11)	66 (19)	19 (6)	10 (4)	<0.001
Primary malignant	306 (35)	88 (26)	117 (38)	101 (44)	n.s.
Metastases	477 (54)	187 (55)	173 (56)	117 (51)	n.s.
Benign tumors					
Hemangioma	27 (3)	14 (4)	10 (3)	3 (1)	
FNH[a]	15 (2)	15 (4)	0	0	
Adenoma	9 (1)	9 (3)	0	0	
Cyst	6 (1)	1 (0)	4 (1)	1 (0)	
Echinococcosis	19 (2)	14 (4)	4 (1)	1 (0)	
Others	19 (2)	13 (4)	1 (0)	5 (2)	
Primary malignant tumors					
Hepatocellular carcinoma	168 (19)	44 (13)	65 (21)	59 (26)	
Cholangiocarcinoma	79 (9)	25 (7)	32 (10)	22 (10)	
Klatskin tumor	38 (4)	13 (4)	15 (5)	10 (4)	
Gallbladder carcinoma	21 (2)	6 (2)	5 (2)	10 (4)	
Metastases					
Colorectal, synchronous	102 (12)	40 (12)	32 (10)	30 (13)	
Colorectal, metachronous	194 (22)	57 (17)	88 (28)	49 (21)	
Neuroendocrine	23 (3)	14 (4)	5 (2)	4 (2)	
Non-colorectal, non-neuroendocrine	158 (18)	76 (22)	48 (16)	34 (15)	
Comorbidities					
ASA >2	537 (61)	176 (51)	200 (65)	161 (71)	<0.001
Charlson comorbidity index	2.77±1.19	2.38±0.79	2.89±1.30	3.12±1.31	<0.001
Cardiovascular	127 (14)	13 (3)	53 (17)	61 (27)	<0.001
Arterial hypertension	266 (30)	63 (18)	105 (34)	108 (47)	<0.001
Pulmonary	31 (4)	9 (3)	13 (4)	9 (4)	n.s.
Diabetes mellitus	117 (13)	18 (5)	47 (15)	52 (23)	<0.001
BMI >30 kg/m^2	134 (15)	42 (12)	45 (15)	47 (21)	n.s.
Previous chemotherapy	316 (36)	128 (37)	117 (38)	71 (31)	n.s.
Underlying liver disease					
Steatosis	396 (45)	136 (40)	151 (49)	109 (48)	n.s.
Fibrosis	202 (23)	76 (22)	66 (21)	60 (26)	n.s.
Cirrhosis	79 (9)	23 (7)	35 (11)	21 (9)	n.s.
Child-Pugh A	77 (9)	22 (6)	34 (11)	21 (9)	
Child-Pugh B	2 (0)	1 (0)	1 (0)	0	
Chronic hepatitis B	29 (3)	13 (4)	11 (4)	5 (2)	n.s.
Chronic hepatitis C	36 (4)	19 (6)	10 (3)	7 (3)	n.s.
Serum bilirubin [mg/dl]	1.93±4.2	1.41±3.1	2.8±3.1	1.37±3.5	<0.001
Serum bilirubin elevated[b]	164 (19)	47 (14)	80 (26)	37 (16)	<0.01
Serum cholinesterase activity [kU/L]	7.2±2.0	7.2±2.0	7.1±2.0	7.1±2.3	n.s.
Resected liver volume [mL]	365±468	404±558	340±397	343±408	n.s.
Tumor diameter [mm]	52.3±55,8	58.3±63.2	47.4±48.2	50.2±53.8	n.s.

Table 1 (continued)

	All patients n=879 (%)	Age <60 years (YP) n=342 (%)	Age 60–69 years (YO) n=309 (%)	Age ≥70 years (EP) n=228 (%)	p value
R status					
R1	65 (7)	33 (10)	22 (7)	10 (4)	<0.05
R2	40 (5)	11 (3)	14 (5)	14 (6)	n.s.

n.s. not significant

[a] Focal nodular hyperplasia

[b] Elevated serum bilirubin=>1.8 mg/dL

liver metastases were from colorectal cancer, more often metachronous than synchronous. Except obesity and severe pulmonary comorbidities, there was a significant difference in comorbidities indicated by the ASA score and the Charlson index (p<0.001, respectively), notably as an increase of comorbidities with increasing age. Underlying hepatic parenchymal diseases (steatosis, fibrosis, cirrhosis), however, were diagnosed equally within the three groups. In addition, serum cholinesterase was comparably active. The analyzed serum parameters of liver enzymes and hepatocyte function surrogate markers revealed no differences except for preoperative bilirubin levels, which were elevated in the YO group (p<0.001). In addition, the proportions of patients receiving preoperative chemotherapy did not show a statistical difference. Comparing pathologic and histopathologic findings, resected liver volume and tumor diameter did not differ. Positive resection margins were found in 12 % of all cases. The portion of microscopically positive margins (R1) were found to be higher in YP (10 %) than in YO (7 %) and EP (4 %) (p<0.05). There was no statistical difference in the frequency of R2 resections (EP 6 %; YP 3 %; YO 5 %).

There were also no differences in the extent of hepatectomy (major, minor) as well as (additional) operative procedures as multivisceral resections when stratified into the three age cohorts. There were no differences noted in terms of blood loss and frequency or duration of ischemic maneuvers. In contrast to FFP, allogeneic red blood cells (ABT) had to be applied in more EP (40 %) than YO (30 %) and YP (32 %) (p<0.05). Additionally, the number of ABT units was higher in EP (1.47±2.7) than in YO (1.01±2.9) and YP (1.25±2.8) (p<0.05). Except for 10 patients, transfusions were administered intraoperatively (n=285). Sixty-one patients (7 %) received ABT postoperatively. Complications were assessed in 44 % of all patients. Their prevalence was higher in EP (54 %) than in the younger cohorts (YP 41 %; YO 40 %; p<0.01). This difference was also shown for severe postoperative complications (Clavien-Dindo grade>II; EP 39 %; YO 27 %; YP 26 %; p<0.01). In contrast to surgical complications as postoperative hemorrhage or bile leak, non-surgical complications such as acute coronary syndrome (p<0.001), postoperative respiratory failure (p<0.001), pneumonia (p<0.01), and liver dysfunction or failure (p<0.001) did occur notably more often in EP than in YO and YP. Total hospital length of stay was longer in EP (18.4 days±15.6) than in YO (14.7 days±13.9) and YP (14.7 days±12.4), respectively, (p<0.01). This also applied to the ICU length of stay (p<0.001). In 312 patients, postoperative complications caused extended hospital length of stay, however, frequencies among the age groups did not significantly differ (EP: 40 %; YO: 33 %; YP: 35 %; p=0.220). Furthermore, proportionately more EP (58 %) were treated on the ICU than YO (48 %) and YP (38 %) (p<0.001), and readmission rates were higher in the elderly (EP 4 %; YO 6 %; YP 11 %; p=0.001).

Postoperative Morbidity (PM)

Univariate analysis of factors influencing PM (Table 3) revealed that advanced age (EP) was highly significantly associated (p<0.001), whereas age, when analyzed as a continuous variable, was not significantly related (p=0.058). Multivariately adjusted for associated factors as comorbidities (CCI>2; p=0.001), major hepatectomy (p<0.001), perioperative ABT (p<0.001), and liver cirrhosis (p=0.006), high age was not independently associated with PM (Table 4; p=0.086). In this proportional model, severe comorbidities (CCI>2; p=0.002; OR 1.66; 95 % CI 1.34–2.03) and major intraoperative blood loss were the only factors being independently related (p=0.039; OR 1.42; 95 % CI 1.02–1.99).

Operative Death and Overall Survival (OS)

Thirty-day mortality rate of all patients was 8 %. In EP, it was higher (14 %) than in YO (7 %) and YP (5 %) (p=0.001). Median survival of all patients was 59 months, 37 months in EP, and 60 months in YO; it was not accomplished by YP. The 1-year survival rate was 83 % in all patients (EP 70 %; YO 84 %; YP 86 %). After 5 years, 50 % of all patients survived, 31 % of EP, 50 % of YO, and 59 % of YP. Log-rank comparison of the three cohorts revealed a significant difference of survival (Fig. 1; p<0.001).

In contrast to morbidity analysis, age higher than 70 years (EP) was not only associated with reduced OS in univariate

Table 2 Surgical procedures and postoperative course (n=879)

	All patients n=879 (%)	Age <60 years (YP) n=342 (%)	Age 60–69 years (YO) n=309 (%)	Age ≥70 years (EP) n=228 (%)	p value
Major hepatectomy	285 (32)	116 (34)	99 (32)	70 (31)	n.s.
Right hepatectomy	121 (14)	49 (14)	42 (14)	30 (13)	
Left hepatectomy	123 (14)	50 (15)	44 (14)	29 (13)	
Extended right hepatectomy	40 (5)	17 (5)	12 (4)	11 (5)	
Extended left hepatectomy	1 (0)	0	1 (0)	0	
Minor hepatectomy	594 (68)	226 (66)	207 (67)	155 (68)	n.s.
Wedge/atypical	348 (40)	131 (38)	121 (39)	96 (42)	
Segmentectomy	91 (10)	30 (9)	38 (12)	23 (10)	
Left lateral sectionectomy (seg. II & III)	65 (7)	27 (8)	14 (5)	24 (11)	
Right posterior sectionectomy (seg. VI & VII)	31 (4)	11 (3)	17 (6)	3 (1)	
Other bisegmentectomy	59 (7)	27 (8)	20 (6)	12 (5)	
Multivisceral resection	224 (25)	91 (27)	73 (24)	60 (26)	n.s.
Ischemic maneuver	191 (22)	82 (24)	67 (22)	42 (18)	n.s.
Duration of ischemic maneuver [min]	4.5±11.1	5.4±12.7	4.3±10.8	3.5±8.8	n.s.
Duration of resection [min]	193.5±90.3	204.0±88.2	188.2±90.3	185.0±86.2	<0.05
Estimated blood loss [mL]	990±1,563	1,086±1,814	856±1,232	1,026±1,551	n.s.
Major blood loss (>1,000 mL)	276 (31)	115 (34)	89 (29)	72 (32)	n.s.
Perioperative blood transfusion (RBC)	295 (34)	109 (32)	94 (30)	92 (40)	<0.05
Perioperative transfusion of fresh frozen plasma (FFP)	196 (22)	82 (24)	58 (19)	56 (25)	n.s.
No. of perioperative RBC	1.23±2.8	1.25±2.8	1.01±2.9	1.47±2.7	<0.05
Total complications	387 (44)	140 (41)	124 (40)	123 (54)	<0.01
Severe complications (Clavien-Dindo>II)	261 (30)	89 (26)	83 (27)	89 (39)	<0.01
Surgical complications					
Secondary hemorrhage	25 (3)	8 (2)	9 (3)	8 (3)	n.s.
Abscess	41 (5)	13 (4)	12 (4)	16 (7)	n.s.
Bile leak/bilioma	56 (6)	31 (9)	13 (4)	12 (5)	n.s.
Wound infection	57 (6)	20 (6)	14 (5)	23 (10)	n.s.
Paralytic ileus	48 (5)	19 (6)	12 (4)	17 (7)	n.s.
Non-Surgical complications					
Acute coronary syndrome	52 (6)	10 (3)	15 (5)	27 (12)	<0.001
Respiratory failure	84 (11)	19 (6)	22 (7)	43 (19)	<0.001
Pneumonia	29 (3)	5 (1)	8 (3)	16 (7)	<0.01
Pleural effusion	54 (6)	14 (4)	12 (4)	28 (12)	n.s.
Liver dysfunction/failure	56 (6)	10 (3)	16 (5)	30 (13)	<0.001
Urogenital infection	22 (2)	9 (3)	4 (1)	9 (4)	n.s.
Total hospital length of stay	15.6±14.0	14.7±12.4	14.7±13.9	18.4±15.6	<0.01
ICU	410 (47)	131 (38)	147 (48)	132 (58)	<0.001
ICU length of stay	2.6±7.7	1.4±3.5	2.4±6.9	5.1±12.1	<0.001
ICU readmission	57 (6)	13 (4)	18 (6)	26 (11)	0.001

n.s. not significant

analysis (p<0.001) but also multivariately (p<0.001; HR 1.88; 95 % CI 1.44–2.37), and when included as a continuous variable (p<0.001). A malignant diagnosis (p<0.001) and the presence of extrahepatic metastases (p<0.001) significantly reduced survival just as stratification into ASA grade 3 or 4 (p<0.001), a CCI >2 (p<0.001), cardiovascular comorbidities (p<0.002), arterial hypertension (p<0.001), severe pulmonary comorbidities (p=0.011), and diabetes mellitus (p<0.001). Kaplan-Meier plots of all age cohorts stratified according to ASA are shown in Fig. 2. In contrast to patients younger than 60 years (p=0.689), the older cohorts featured lowered OS when assigned to the ASA 3 or 4 sub-group (p=0.002 and p=0.039, respectively). Multivariately analyzed, ASA grade 3 or 4 exhibited an HR of 1.51 (p=0.001;

Table 3 Univariate analysis for postoperative morbidity and overall survival

	Morbidity n=879 p value	Survival n=839 p value
Age >70	<0.001	<0.001
Age (continuous)	0.058	<0.001
Gender	0.584	0.171
Diagnosis		
Malignant diagnosis	0.012	<0.001
Metastases vs. primary malignoma	0.222	0.347
Presence of non-hepatic metastases	0.021	<0.001
Comorbidities		
ASA >2	0.020	<0.001
Charlson comorbidity index >2	<0.001	<0.001
Cardiovascular	0.031	0.008
Arterial hypertension	0.055	<0.001
Pulmonary	0.055	0.008
Diabetes mellitus	0.026	<0.001
BMI >30 kgm^{-2}	0.657	<0.001
Previous chemotherapy	0.545	0.875
Underlying liver disease		
Steatosis	0.851	0.827
Fibrosis	0.518	0.692
Cirrhosis (child A and B)	0.006	0.092
Intraoperative parameters		
Major hepatectomy	< 0.001	0.002
Multivisceral resection	0.005	<0,001
Major blood loss (>1,000 mL)	0.001	0.003
Perioperative ABT	< 0.001	<0.001
Ischemic maneuver	0.653	0.662
Pathologic results		
R1/2	0.221	<0.001
Steatosis/cirrhosis	0.383	0.365
Resected liver weight	0.207	<0.001
Tumor diameter	0.114	0.412
Number of liver tumors	0.019	0.417
Postoperative morbidity		
Total complications		<0.001
Severe complications (Clavien-Dindo >II)		<0.001
ICU		<0.001
ICU length of stay		<0.001
Operative revision		<0.001
Surgical complications		
Secondary hemorrhage		0.024
Abscess		<0.001
Bile leak/bilioma		0.040
Wound infection		0.120
Paralytic ileus		0.009
Non-surgical complications		
Acute coronary syndrome		<0.001
Respiratory failure		<0.001
Pneumonia		0.085
Pleural effusion		0.024
Liver dysfunction/failure		<0.001
Urogenital infection		0.414
Postoperative chemotherapy		<0.001

95 % CI 1.18–1.94). Notably, underlying parenchymal liver diseases (steatosis, fibrosis, or cirrhosis) had no negative influence on OS. Major hepatectomy (p=0.025; HR 1.33; 95 % CI 1.04–1.70) and major estimated blood loss (EBL; >1,000 mL; p=0.031; HR 1.32; 95 % CI 1.03–1.69) significantly affected OS. Whereas major EBL (Fig. 3) was associated with comparable OS in YP (p=0.933; Fig. 3b), it was significantly associated with reduced OS in YO (p<0.009; Fig. 3c) and highly significantly in EP (p<0.001; Fig. 3d). Postoperative complications were univariately (p<0.001) and multivariately (p<0.001; HR 1.64; 95 % CI 1.30–2.07) associated with reduced OS in all patients. Within sub-analyses, however, this was the case in EP and YO (p<0.001, respectively) in contrast to YP (p=0.128).

Discussion

Our study identified age >70 years, preexisting comorbidities, major liver resection, increased EBL, and postoperative complications as independent risk factors for reduced overall survival. Independent predictors of postoperative morbidity were comorbidities and major EBL. Our data also show that

Table 4 Multivariate analysis of postoperative morbidity and overall survival

	Postoperative morbidity (n=879)		
	p value	Odds ratio	95 % CI
Age >70 years	0.086	1.49	0.94–2.33
CCI >2	0.002	1.66	1.34–2.03
Major hepatectomy	0.901	1.03	0.67–1.58
Major blood loss	0.039	1.42	1.02–1.99
Cirrhosis	0.139	1.71	0.84–3.49
	Overall survival (n=839)		
	p value	Hazard ratio	95 % CI
Age >70 years	<0.001	1.85	1.44–2.37
ASA >2	0.001	1.51	1.18–1.94
Major hepatectomy	0.025	1.33	1.04–1.70
Major blood loss	0.031	1.32	1.03–1.69
Postoperative complications	<0.001	1.64	1.30–2.07

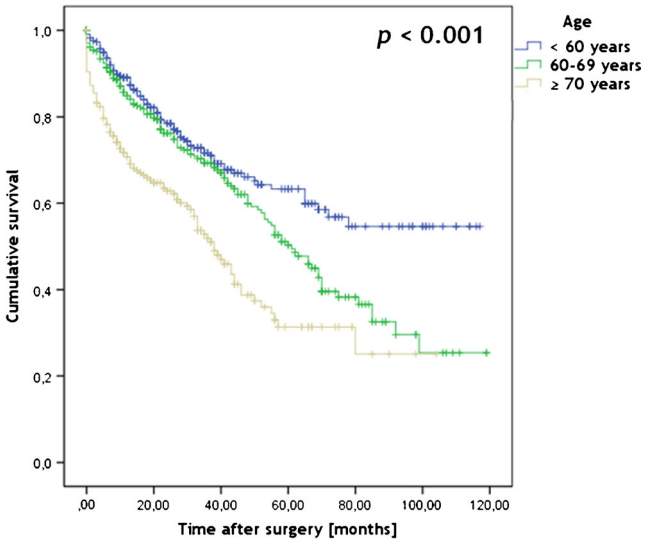


Fig. 1 Overall survival of the three age cohorts. Median survival of all patients was 59 months, for EP 37 months, and for YO 60 months. It was not reached by YP

elderly patients feature a more severe preoperative risk profile and that those preexisting comorbidities (Fig. 2), major EBL (Fig. 3), and postoperative complications particularly endanger patients of advanced age compared to younger ones.

In recent years, the number of elderly patients scheduled for liver surgery has continuously increased.[1–3] Given this progress, the identification of the predictors of PM and OS of this population is of specific interest. From the oncological point of view, it has been demonstrated that elderly patients benefit equally well from liver resection and chemotherapy for the treatment of HCC and colorectal liver metastases compared to younger ones.[26–30] However, the aged are less likely to be treated with chemotherapy[31–36] as well as to undergo resection for colorectal liver metastases.[37–39] The retentiveness regarding liver resection in aged patients may be explained by the increased perioperative risk in this population. Therefore, it is necessary to identify age-specific risk factors for perioperative morbidity and decreased survival. This may improve perioperative management and enable surgeons to select those elderly who benefit the most from liver resection.

In our study population, high age was associated with increased perioperative death and a higher incidence of severe and non-surgical complications. Advanced age was associated with a higher prevalence of preexisting comorbidities which is in line with previous published studies.[5,7,12,14,16,17,40] ASA grade > 2 and CCI >2, featuring a higher prevalence in EP,[8,10] were associated with increased morbidity and reduced survival. This is in accordance with a large study of Menon et al.[10]

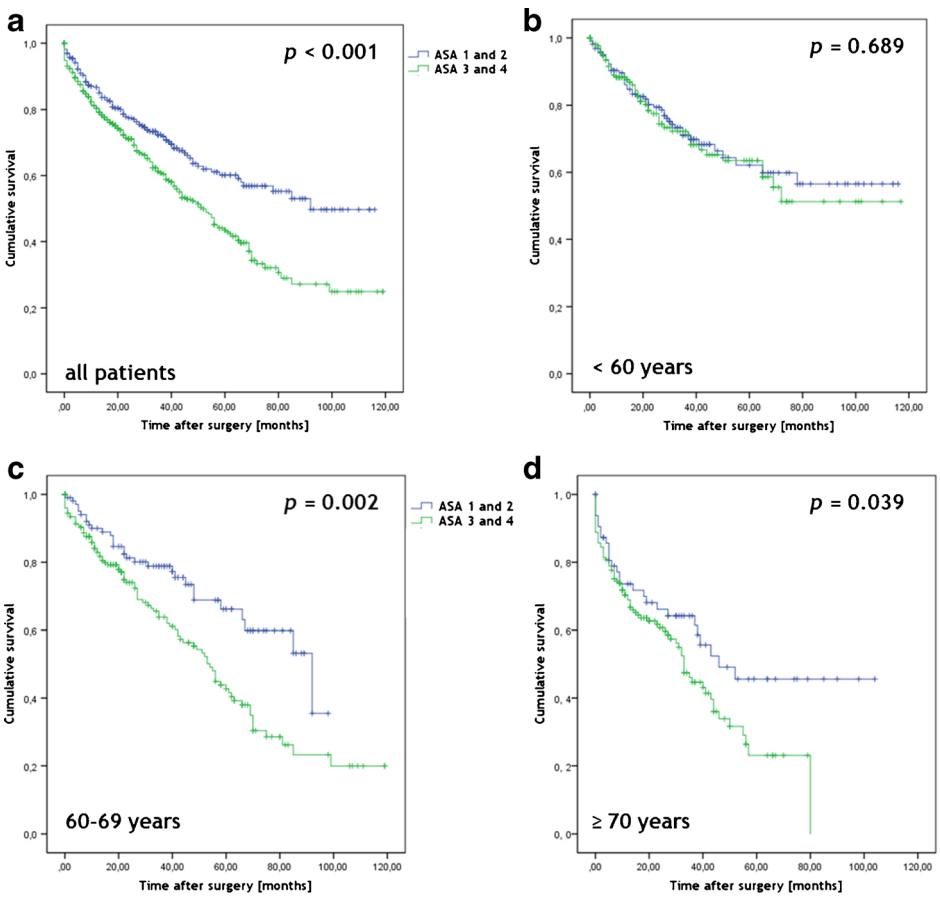


Fig. 2 Overall survival according to ASA classification (**a**) and after stratification into the three age cohorts YP (**b**), YO (**c**), and EP (**d**)

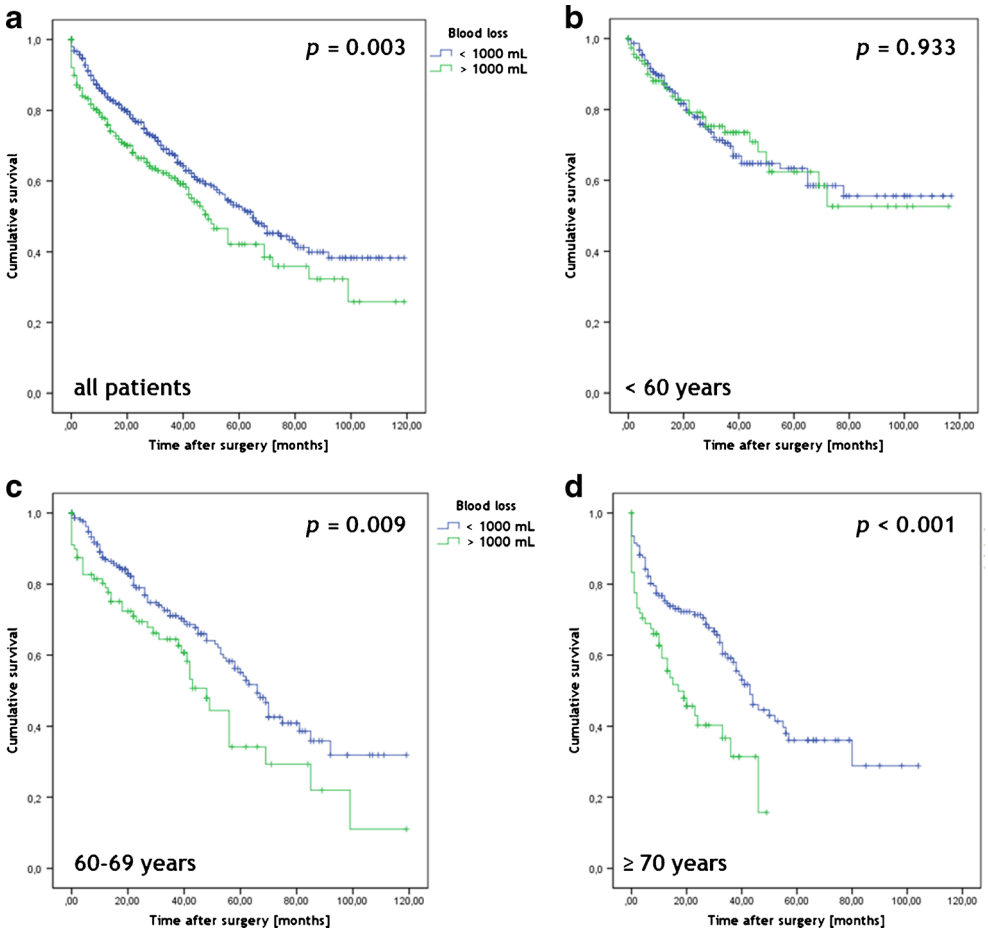


Fig. 3 Overall survival according to the extent of estimated intraoperative blood loss (<1,000 vs. >1,000 mL) (**a**) and after stratification into the three age cohorts YP (**b**) HR, YO (**c**), and EP (**d**)

Furthermore, our findings amend the observations of Fong and colleagues linking a high ASA grade with a poor outcome.[3] This impact of comorbidities on PM and OS increases with age (Fig. 2): In contrast to YP (Fig. 2b), patients 60 years and older (Fig. 2c, d) featuring ASA grade >2 displayed reduced OS compared to their healthier counterparts within the same age cohort. Better outcome in younger patients may result from higher perioperative compensatory capacities. Hence, ASA grading seems to predict outcome more precisely for the aged population.[3,9,15,18,41] Our data outline the significance of this score for patients 60 years and older.

Compared to younger patients (7 and 5 %, respectively), EP featured a higher 30-day mortality rate (14 %). Other studies showed a large variation in mortality rates ranging from below 5 % to more than 40 %.[3,8,9,13,15,18,19,42] While some studies showed similar morbidity and mortality rates in young and aged patients,[2,3,9] we and others found a higher risk for the elderly.[10,19,43,44] The most frequently reported causes of operative death are hepatic failure, acute coronary syndrome, respiratory failure, and gastrointestinal bleeding.[3,18,44,45] We found similar causes as follows: 55 % of the EP deceasing within the first 30 days after surgery died from acute coronary syndrome and consecutive heart failure, 19 % from primary hepatic failure, and 10 % from primary respiratory failure. This again emphasizes the importance of preoperative cardiac assessment.

In our population, EP underwent equally often major liver resections compared to younger patients. This is noteworthy since aged patients are more likely to require extended resections for total surgical tumor exstirpation.[1,3,9,14] When a major resection was performed, it increased morbidity and decreased survival. In conjunction with this, major intraoperative blood loss (EBL) was also an independent risk factor for both morbidity and reduced survival. Although EBL did not differ between the age cohorts, perioperative ABT was significantly more frequent in EP. In addition, more ABT units were administered. This is in accordance with previous published data[11,40] and might be due to a lower transfusion trigger applied in patients with cardiovascular disease. Regarding the cohorts' sub-analyses (Fig. 3), major EBL particularly endangers the aged compared to younger patients. Hence, the reduction of blood loss seems to play an even more decisive role in aged patients affecting early and late outcomes. This might be due to minor cardiopulmonary compensatory resources.[11] These findings emphasize strategies of

blood loss minimization such as preoperative autologous blood donation and intraoperative approaches as administration of tranexamic acid and adherence to a low central venous pressure (≤6 mmHg). Ischemic maneuvers (temporary hepatic vascular inflow occlusion) were not associated with morbidity (p=0.653) and overall survival (p=0.662) in the present study. A more liberal application might be another option to avoid blood loss just as ultrasonic parenchyma dissection or intraoperative cell saving techniques.[46]

In the literature, overall complication rates range from 30 to 50 %.[1,2,5,8,10,26] In our study, it was 44 %. EP were at higher risk for non-surgical but not surgical complications. This phenomenon has been previously observed[11,47] but has not been satisfactorily clarified. Comorbidities (i.e., coronary artery disease) may increase the risk of non-surgical complications (i.e., acute coronary syndrome) in contrast to surgical morbidity which might occur due to age-independent factors. Notably, elderly patients featured a longer hospital length of stay which tended to be associated with higher rates of non-surgical and severe complications. Prolonged hospital stay may also be caused by extended postoperative routine monitoring on the ICU as well as longer surveillance and recovering from hepatic resection. In fact, postoperative complications lead to a higher rate of ICU readmissions in elderly patients compared to younger ones (Table 2). The incidence of postoperative complications was an independent risk factor for reduced OS.[12,48] Like blood loss, this is age-dependent (YP and YO p<0.001, respectively; YP p=0.128), probably due to reduced compensation and recovery mechanisms in the elderly as well. Whereas comparable morbidity rates between older and younger patients have been reported, it was concurrently shown that the elderly are less likely to recover from those complications.[1,7–11]

Though advanced age was a predictor for reduced survival, it did not the increase postoperative morbidity in the multivariate analysis when adjusted for comorbidities (Table 4). This emphasizes the catchphrase "Geriatric surgery is about disease, not age".[49] Altogether, our data indicate the importance of adequately addressing the patient's comorbidities during perioperative care in the aged in order to prevent cardiovascular and pulmonary postoperative events.[3,9,15,18]

Conclusion

Elderly patients scheduled for liver resection were more likely to suffer from comorbidities. They had a higher incidence of non-surgical complications and an increased postoperative mortality. Preexisting comorbidities and putatively lower physiologic reserves seem to result in a decreased capacity to compensate major intraoperative blood loss and to recover from postoperative complications in this population. Blood loss is a crucial factor independently increasing morbidity and mortality especially endangering aged patients. Thus, key points for the selection of elderly patients for liver resections are the identification of associated comorbidities, reduction of intraoperative blood loss, and the diligent prevention of postoperative complications. No limitations should be ordained based exclusively on the patient's age, but appropriate patient selection may improve the elderly's outcome given the fact that this population is more likely to suffer from associated diseases.

Acknowledgments The authors thank Professor Horst Domdey for critically revising the manuscript and Dr. Hans-Martin Hornung for his dedicated work with the IT administration of the liver database.

Conflicts of Interests There was no funding received for the present study. There are no financial or personal conflicts of any of the authors.

References

1. Reddy SK, Barbas AS, Turley RS, Gamblin TC, Geller DA, Marsh JW, Tsung A, Clary BM, Lagoo-Deenadayalan S. Major liver resection in elderly patients: a multi-institutional analysis. J Am Coll Surg 2011;212:787–795.
2. Melloul E, Halkic N, Raptis DA, Tempia A, Demartines N. Right hepatectomy in patients over 70 years of age: an analysis of liver function and outcome. World J Surg 2012.
3. Fong Y, Brennan MF, Cohen AM, Heffernan N, Freiman A, Blumgart LH. Liver resection in the elderly. Br J Surg 1997;84:1386–1390.
4. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758–2765.
5. Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N, Adachi W, Amano J. Hepatic resection for hepatocellular carcinoma in the elderly. J Am Coll Surg 2001;192:38–46.
6. Pasetto LM, Lise M, Monfardini S. Preoperative assessment of elderly cancer patients. Crit Rev Oncol Hematol 2007;64:10–18.
7. Aldrighetti L, Arru M, Caterini R, Finazzi R, Comotti L, Torri G, Ferla G. Impact of advanced age on the outcome of liver resection. World J Surg 2003;27:1149–1154.
8. Cescon M, Grazi GL, Del GM, Ercolani G, Ravaioli M, Nardo B, Cavallari A. Outcome of right hepatectomies in patients older than 70 years. Arch Surg 2003;138:547–552.
9. Ettorre GM, Sommacale D, Farges O, Sauvanet A, Guevara O, Belghiti J. Postoperative liver function after elective right hepatectomy in elderly patients. Br J Surg 2001;88:73–76.
10. Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after major hepatectomy in elderly patients. J Am Coll Surg 2006;203:677–683.
11. Shirabe K, Kajiyama K, Harimoto N, Gion T, Tsujita E, Abe T, Wakiyama S, Nagaie T, Maehara Y. Early outcome following hepatic resection in patients older than 80 years of age. World J Surg 2009;33:1927–1932.
12. Lee CR, Lim JH, Kim SH, Ahn SH, Park YN, Choi GH, Choi JS, Kim KS. A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients. J Gastrointest Surg 2012;16:1736–1743.
13. Ezaki T, Yukaya H, Ogawa Y. Evaluation of hepatic resection for hepatocellular carcinoma in the elderly. Br J Surg 1987;74:471–473.

14. Koperna T, Kisser M, Schulz F. Hepatic resection in the elderly. World J Surg 1998;22:406–412.
15. Mentha G, Huber O, Robert J, Klopfenstein C, Egeli R, Rohner A. Elective hepatic resection in the elderly. Br J Surg 1992;79:557–559.
16. Nagasue N, Chang YC, Takemoto Y, Taniura H, Kohno H, Nakamura T. Liver resection in the aged (seventy years or older) with hepatocellular carcinoma. Surgery 1993;113:148–154.
17. Tsujita E, Utsunomiya T, Ohta M, Tagawa T, Matsuyama A, Okazaki J, Yamamoto M, Tsutsui S, Ishida T. Outcome of repeat hepatectomy in patients with hepatocellular carcinoma aged 75 years and older. Surgery 2010;147:696–703.
18. Wu CC, Chen JT, Ho WL, Yeh DC, Tang JS, Liu TJ, P'eng FK. Liver resection for hepatocellular carcinoma in octogenarians. Surgery 1999;125:332–338.
19. Takenaka K, Shimada M, Higashi H, Adachi E, Nishizaki T, Yanaga K, Matsumata T, Ikeda T, Sugimachi K. Liver resection for hepatocellular carcinoma in the elderly. Arch Surg 1994;129:846–850.
20. Von EE, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370: 1453–1457
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
22. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg 2005;12:351–355.
23. Hardy JF. Current status of transfusion triggers for red blood cell concentrates. Transfus Apher Sci 2004;31:55–66.
24. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.
25. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–196.
26. Adam R, Frilling A, Elias D, Laurent C, Ramos E, Capussotti L, Poston GJ, Wicherts DA, de Haas RJ. Liver resection of colorectal metastases in elderly patients. Br J Surg 2010;97:366–376.
27. Zacharias T, Jaeck D, Oussoultzoglou E, Bachellier P, Weber JC. First and repeat resection of colorectal liver metastases in elderly patients. Ann Surg 2004;240:858–865.
28. Turrini O, Guiramand J, Moutardier V, Viret F, Bories E, Giovannini M, Mokart D, Blache JL, Delpero JR. [Major hepatectomy for metastasis of colorectal cancer improves survival in the elderly]. Ann Chir 2005;130:562–565.
29. Ferrero A, Vigano L, Polastri R, Ribero D, Lo TR, Muratore A, Capussotti L. Hepatectomy as treatment of choice for hepatocellular carcinoma in elderly cirrhotic patients. World J Surg 2005;29:1101–1105.
30. Yeh CN, Lee WC, Jeng LB, Chen MF. Hepatic resection for hepatocellular carcinoma in elderly patients. Hepatogastroenterology 2004;51:219–223.
31. Neugut AI, Fleischauer AT, Sundararajan V, Mitra N, Heitjan DF, Jacobson JS, Grann VR. Use of adjuvant chemotherapy and radiation therapy for rectal cancer among the elderly: a population-based study. J Clin Oncol 2002;20:2643–2650.
32. Yee KW, Pater JL, Pho L, Zee B, Siu LL. Enrollment of older patients in cancer treatment trials in Canada: why is age a barrier?. J Clin Oncol 2003;21:1618–1623.
33. Jessup JM, Stewart A, Greene FL, Minsky BD. Adjuvant chemotherapy for stage III colon cancer: implications of race/ethnicity, age, and differentiation. JAMA 2005;294:2703–2711.
34. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061–2067.
35. Unger JM, Coltman CA, Jr., Crowley JJ, Hutchins LF, Martino S, Livingston RB, Macdonald JS, Blanke CD, Gandara DR, Crawford ED, Albain KS. Impact of the year 2000 Medicare policy change on older patient enrollment to cancer clinical trials. J Clin Oncol 2006;24:141–144.
36. Kahn KL, Adams JL, Weeks JC, Chrischilles EA, Schrag D, Ayanian JZ, Kiefe CI, Ganz PA, Bhoopalam N, Potosky AL, Harrington DP, Fletcher RH. Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. JAMA 2010;303:1037–1045.
37. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254–259.
38. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006;93:465–474.
39. Mirici-Cappa F, Gramenzi A, Santi V, Zambruni A, Di MA, Frigerio M, Maraldi F, Di Nolfo MA, Del PP, Benvegnu L, Rapaccini G, Farinati F, Zoli M, Borzio F, Giannini EG, Caturelli E, Bernardi M, Trevisani F. Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-year multicentre experience. Gut 2010;59:387–396.
40. Al-Refaie WB, Parsons HM, Henderson WG, Jensen EH, Tuttle TM, Vickers SM, Rothenberger DA, Virnig BA. Major cancer surgery in the elderly: results from the American College of Surgeons National Surgical Quality Improvement Program. Ann Surg 2010;251:311–318.
41. Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y, Kubota K, Zucchi A. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. Arch Surg 1999;134:984–992.
42. Yamamoto K, Takenaka K, Matsumata T, Shimada M, Itasaka H, Shirabe K, Sugimachi K. Right hepatic lobectomy in elderly patients with hepatocellular carcinoma. Hepatogastroenterology 1997;44: 514–518.
43. Yanaga K, Kanematsu T, Takenaka K, Matsumata T, Yoshida Y, Sugimachi K. Hepatic resection for hepatocellular carcinoma in elderly patients. Am J Surg 1988;155:238–241.
44. Fortner JG, Lincer RM. Hepatic resection in the elderly. Ann Surg 1990;211:141–145.
45. Melendez J, Ferri E, Zwillman M, Fischer M, DeMatteo R, Leung D, Jarnagin W, Fong Y, Blumgart LH. Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. J Am Coll Surg 2001;192:47–53.
46. Bui LL, Smith AJ, Bercovici M, Szalai JP, Hanna SS. Minimising blood loss and transfusion requirements in hepatic resection. HPB (Oxford) 2002;4:5–10.
47. Duron JJ, Duron E, Dugue T, Pujol J, Muscari F, Collet D, Pessaux P, Hay JM. Risk factors for mortality in major digestive surgery in the elderly: a multicenter prospective study. Ann Surg 2011;254:375–382.
48. Mavros MN, de JM, Dogeas E, Hyder O, Pawlik TM. Impact of complications on long-term survival after resection of colorectal liver metastases. Br J Surg 2013;100:711–718.
49. Preston SD, Southall AR, Nel M, Das SK. Geriatric surgery is about disease, not age. J R Soc Med 2008;101:409–415.