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Transorale Lasermikrochirurgie im Gesamtkonzept multimodaler Therapiestrategien für Kopf-Hals-Karzinome

Kumulative Habilitationsschrift
zur Erlangung der Venia Legendi
in der Hals-, Nasen-, Ohrenheilkunde

vorgelegt von
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Abkürzungsverzeichnis

EORCT	*European Organization for Research and Treatment of Cancer*
ND	Neck dissection
RCT	Radiochemotherapie
R(C)T	Radio(chemo)therapie
SCAIF	supraclavikuläres Inseltransplantat
TLM	Transorale Lasermikrochirurgie

Anmerkung

Eine Reihe der im Rahmen des kumulativen Habilitationsprojekts vorgestellten Forschungsarbeiten sind im Rahmen meiner klinischen und wissenschaftlichen Tätigkeit an der Universitätsmedizin Göttingen entstanden. Im Folgenden wird nicht weiter auf den Ursprung beispielsweise beschriebener Patientenkollektive eingegangen. Hierzu wird auf die Originalarbeiten verwiesen.

Alle im Folgenden genannten Informationen zu TNM-Klassifikation und Tumorstadien entsprechen den Staging-Kriterien der 7. Edition der *Union International Contre le Cancer* (UICC) (Sobin and Compton, 2010) bzw. des *American Joint Committee on Cancer* (AJCC) (Edge and Compton, 2010).

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1 Einleitung

Die Behandlung von Kopf-Hals-Karzinomen erfordert individuelle stadiengerechte Therapiekonzepte, die heute im Rahmen interdisziplinärer Tumorkonferenzen im Konsens festgelegt werden. Trotz der Häufigkeit von 16.330 Neuerkrankungen an Tumoren von Mundhöhle, Rachen und Larynx in Deutschland pro Jahr (Robert-Koch-Institut, 2017) gibt es insbesondere im internationalen Vergleich divergierende Therapiekonzepte. Behandlungsstrategien umfassen chirurgische, radio- und chemotherapeutische Therapiemodalitäten. Für die Behandlung des Primärtumors hat sich in einigen Zentren als Alternative zu konventionell chirurgischen Verfahren die transorale CO_2-Lasermikrochirurgie (TLM) etabliert. Falls indiziert wird die primär chirurgische Therapie durch eine Neck dissection, rekonstruktionschirurgische Verfahren und eine adjuvante Radio(chemo)therapie ergänzt. Eine Alternative zum primär chirurgischen Behandlungskonzept stellt die primäre Radio(chemo)therapie dar (Bourhis et al., 2012; Beitler et al., 2014).

Die minimalinvasive transorale CO_2-Lasermikrochirurgie (TLM), initial von Strong und Jako zur Behandlung von benignen Läsionen des Larynx eingeführt (Strong and Jako, 1972), wurde durch Professor Steiner und Kollegen in Göttingen von kleinen zu ausgedehnten Tumoren (T1 – 4a) und auf alle Regionen des Larynx, des Oro- und Hypopharynx sowie der Mundhöhle erweitert (Steiner, 1988; Steiner and Ambrosch, 2000; Steiner, 2013). Aufgrund des transoralen Zugangs erlaubt die Lasermikrochirurgie gegenüber der konventionellen Chirurgie eine maximale Schonung nicht befallenen Gewebes. Darüber hinaus verspricht die schrittweise Resektion des Tumors unter mikroskopischer Sicht eine akkurate Inspektion der Grenzen zwischen Tumor- und Normalgewebe, wobei durch die Beurteilung des Schneideverhaltens (u. a. Grad der Karbonisierung) eine Differenzierung zwischen Tumor- und Normalgewebe ermöglicht wird. Hierdurch gelingt es die Tumorinfiltrationstiefe zu bestimmen einen ausreichenden Sicherheitsabstand zu wahren und dabei bestmöglich gesundes Gewebe zu erhalten (Steiner, 1988; Steiner and Ambrosch, 2000; Steiner, 2013). Nicht zuletzt werden durch den Schnitt mit dem Laserstrahl kleine Gefäße simultan verödet, was zu blutarmen Operationsbedingungen führt und zudem eine Aussaht von Tumorzellen zu verhindern scheint (Wiegand et al., 2013).

Ziele der Tumortherapie sind die höchstmögliche onkologische Sicherheit, der bestmögliche Funktionserhalt, eine geringe Komplikationsrate sowie nicht zuletzt eine hohe gesundheitsbezogene Lebensqualität. Bisher existieren keine prospektiven randomisierten Studien, die unter Berücksichtigung all dieser Anforderungen an die Tumortherapie die Überlegenheit einer Therapiestrategie eindeutig darstellen.

2 Zielsetzung und Fragestellungen

Die vorliegende Habilitationsarbeit befasst sich mit der transoralen Lasermikrochirurgie zur Behandlung von Kopf-Hals-Malignomen. Untersucht werden für Tumoren des Larynx, des Oro- und des Hypopharynx die onkologischen und funktionellen Ergebnisse, das postoperative Management sowie die Komplikationsrate dieser primär chirurgischen Therapie. Bei den Untersuchungen zur primären TLM in der Behandlung von Oropharynxkarzinomen soll entsprechend der aktuellen Diskussion auch der p16 Status als prognostischer Faktor berücksichtigt werden. Aufgrund des nicht unerheblichen Anteils von Erkrankungen, die bei Erstdiagnose bereits ein fortgeschrittenes Stadium erreicht haben liegt ein besonderer Fokus auf der Darstellung der TLM im Gesamtkonzept multimodaler Therapiestrategien. Zudem wird die TLM im Kontext der Rezidivsituation untersucht. Weiterhin befasst sich die Arbeit mit rekonstruktionschirurgischen Verfahren, die ergänzend zur TLM eine Verbesserung der Funktion und der Lebensqualität zum Ziel haben. Eine enge Zusammenarbeit mit der Pathologie ist essentiell in der chirurgischen Tumortherapie. Hierzu wird insbesondere die Art der Technik zur histopathologischen Bestätigung einer vollständigen Tumorresektion (R0) sowie die Auswirkung eines histopathologisch positiven Residualtumors (R1) untersucht. In den dieser kumulativen Habilitationsschrift zugrundeliegenden Arbeiten wurden hierzu die folgenden Fragestellungen bearbeitet:

1. Welchen Stellenwert hat die transorale Lasermikrochirurgie in der Behandlung von frühen glottischen Larynxkarzinomen?
   (Weiss et al., 2017c)
2. Welchen Stellenwert hat die transorale Lasermikrochirurgie in der primären Behandlung von frühen und fortgeschrittenen Tumoren des Oro- und Hypopharynx?
   (Weiss et al., 2017b; Weiss et al., 2019)
3. Welche Rolle spielt der immunhistochemisch bestimmte p16 Status als prognostischer Faktor bei Oropharynxkarzinomen?
   (Weiss et al., 2019)
4. Welchen Stellenwert hat die multimodale Therapie im Rahmen eines TLM-basierten Behandlungskonzeptes für eine fortgeschrittene Tumorerkrankung?
   (Weiss et al., 2017b; Weiss et al., 2019)
5. Ist die transorale Lasermikrochirurgie eine Therapieoption von Larynxkarzinomen in der Rezidivsituation?
   (Weiss et al., 2017a)

6. Welchen Stellenwert haben rekonstruktionschirurgische Verfahren in der Behandlung lokal fortgeschrittener Tumoren der Mundhöhle und des Oropharynx?
    a. Führt die Rekonstruktion mittels freiem Radialistransplantat nach partieller Glossektomie bei pT3 Zungenrandkarzinomen zu einer besseren gesundheitsbezogene Lebensqualität?
    (Canis et al., 2016)
    b. Eignet sich neben dem freien mitrovaskulär anastomosierten Radialistransplantat auch das gestielte supraclavikuläre Inseltransplantat zur Rekonstruktion von Defekten der Mundhöhle und des Oropharynx?
    (Welz et al., 2017)
7. Welche Bedeutung hat die histopathologische Bestätigung einer vollständigen Tumorresektion (R0) auf die onkologischen Ergebnisse in der chirurgischen Tumortherapie?
    a. Hat die Methode der Randprobengewinnung Einfluss auf die onkologischen Ergebnisse?
    (Maxwell et al., 2015)
    b. Welchen Stellenwert haben erzielbarer Resektionsstatus und Behandlungsstrategie auf die onkologischen Ergebnisse von Gehörgangskarzinomen?
    (Ihler et al., 2015)

3 Ergebnisse und Diskussion der zugrundeliegenden Originalarbeiten

3.1 Transorale Lasermikrochirurgie bei frühen glottischen Larynxkarzinomen

Glottische Larynxkarzinome haben gegenüber den anderen Tumorlokalisationen eine bessere Prognose, da Patienten früh Symptome wie Dysphonie aufweisen. Darüber hinaus befinden sich in dieser Region kaum Lymphgefäße, folglich ist eine lymphogene Metastasierung rar (Werner et al., 1995). Dies bestätigte sich auch in unserem Kollektiv. Bei 455 untersuchten Fällen mit einem primär lasermikrochirurgisch behandelten T1 glottischen Larynxkarzinom lag bei Erstdiagnose keine Lymphknotenmetastasierung vor. Auch kam es zu keinem isolierten regionären Rezidiv im Sinne einer Spätmetastase (Canis et al., 2014a; Weiss et al., 2017c). Hingegen lag bei Erstdiagnose von kleinen T1 Hypopharynxkarzinomen bereits zu 61 % eine zervikale Metastasierung vor und verglichen mit den T1 glottischen Larynxkarzinomen zeigten sich bei dieser Gruppe geringere Überlebensraten (Canis et al., 2014a; Weiss et al., 2017c; Weiss et al., 2017b).

Meist manifestieren sich frühe glottische Larynxkarzinome unilateral eine Stimmlippe betreffend (T1a). Deutliche seltener liegt ein bilateraler Befall bzw. eine Infiltration der vorderen Kommissur vor (T1b). Im Vergleich der Gruppe von 51 T1b-Fällen mit den deutliche häufiger auftretenden T1a-Karzinomen wurden für diese ausschließlich lasermikrochirurgisch behandelten Patienten folgende onkologischen Ergebnisse beobachtet: Die 5-Jahres lokale Kontrollrate lag bei 90,2 % für T1b vs. 86,8 % für T1a, das 5-Jahres Gesamtüberleben bei 84,7 % für T1b vs. 87,8 % für T1a, das krankheitsspezifische Überleben bei 97,7 vs. 98,0%, und das Rezidiv-freie Überleben bei 72,4 vs. 76,1 % (Canis et al., 2014a; Weiss et al., 2017c).

Alternative Behandlungsstrategien zur TLM sind die konventionell-offene Larynxteilresektion oder die primäre Radiotherapie (Karatzanis et al., 2009; Hirasawa et al., 2012; Lei et al., 2013). Die onkologischen Ergebnisse der transoralen Lasermikrochirurgie sind mit diesen Alternativen wenigstens vergleichbar, wenngleich ein direkter Vergleich retrospektiver Untersuchungen nur eingeschränkt möglich ist. Unterschiede in Tumorstadien, Definition der Endpunkte, Untersuchungszeiträume, statistische Methoden und Einschlusskriterien für diverse Behandlungsmodalitäten müssen bei der Bewertung berücksichtigt werden. Bis heute fehlen jedoch randomisierte kontrollierte klinische Studien, welche die TLM mit anderen Therapiestrategien vergleichen (Warner et al., 2014).

Der große Vorteil des transoralen Zugangs ist das geringe Trauma für gesundes Gewebe. Im Gegensatz dazu erfordert die konventionelle offene Chirurgie zur Exposition des Tumors eine Dissektion durch Cutis, Subcutis und prälaryngealer Muskulatur mit zudem Unterbrechung der Integrität des Larynxskelettes. Folglich geht das schonendere transorale Vorgehen mit deutlich weniger Komplikationen einher. Lei et al. verglichen die mittlere frontal-horizontale partielle Laryngektomie

mit der anterioren frontolateral-vertikalen partiellen Laryngektomie zur Behandlung der T1b Larynxkarzinome. Die onkologischen Ergebnisse waren mit unseren vergleichbar, wohingegen schwere Komplikationen wie Larynxfisteln (5,9 %) und laryngeale Stenosen (17,6 %) nach der zweiten Operationstechnik und subcutane Emphyseme, Aspiration und Pneumonien nach beiden Arten der partiellen Laryngektomie aufgetreten waren (Lei et al., 2013). In einer vergleichenden retrospektiven Analyse wurde gezeigt, dass Komplikationen nach TLM im Vergleich zur offenen Chirurgie deutlich seltener auftraten (Karatzanis et al., 2009). Bei unseren 51 ausschließlich lasermikrochirurgisch behandelten T1b-Patienten kam es in nur in einem Fall zur Ausbildung einer Synechie. Andere Komplikationen wurde nicht beobachtet. Auch musste keine Tracheotomie oder Einlage einer nasogastralen Sonde erfolgen (Weiss et al., 2017c), das -wenn auch meist nur temporär- nach offenen Eingriffen obligat erforderlich war (Pignataro et al., 2000; Lei et al., 2013). Eine schnelle Genesung und kurze Krankenhausverweildauer sind folglich weitere Vorteile der TLM (Altuna et al., 2005). Dies gilt auch im Vergleich zur primären Radiotherapie, die eine Serie täglicher Behandlungen über meist 6 Wochen erfordert. Komparative retrospektive Analysen zu glottischen T1 Karzinomen die mittels primärer Radiotherapie oder TLM behandelt wurden kommen zu widersprüchlichen Aussagen. Sie präsentieren zum einen signifikante Unterschiede im onkologischen Ergebnis und empfehlen die Chirurgie (Markou et al., 2002) oder konstatieren ein äquivalentes Ergebnis (Dinapoli et al., 2010).
Insbesondere bei frühen Larynxkarzinomen haben im Vergleich zur primären Radiotherapie chirurgische Strategien jedoch folgende weitere Vorteile.

1. Ein histologisch bestätigte R0-Resektion kann erzielt werden
2. Im Falle eines Rezidivs ist ein erneuter chirurgischer Ansatz (auch TLM (Weiss et al., 2017a)) eine mögliche Therapieoption aber auch radiotherapeutische Strategien (adjuvant oder primär) stehen zur Verfügung. Im Gegensatz dazu ist nach initial primärer Radiotherapie im Falle eines Residual- oder Rezidivtumors die einzig verbleibende Therapieoption eine chirurgische
3. Bei primär chirurgisch/TLM therapierten Patienten trifft die erneute chirurgische Behandlung im Falle eines Rezidivs auf unbestrahltes Gewebe und aufgrund des vorausgegangenen geringen Gewebetraumas nach TLM auf auch chirurgisch nahezu unberührtes Gewebe. Zudem ist eine Tracheotomie -im Rahmen konventioneller Chirurgie häufig- während der TLM meist nicht erforderlich. Beides, eine vorausgegangene Bestrahlung aber auch eine Tracheotomie sind als Risikofaktoren für schwere Komplikationen wie pharyngokutane Fisteln identifiziert (Paydarfar and Birkmeyer, 2006)

3.2 Transoralen Lasermikrochirurgie für Tumoren des Oro- und Hypopharynx

Auch für Karzinome des Oro- und Hypopharynx stellt die primäre transorale Lasermikrochirurgie eine Behandlungsoption dar. Falls indiziert wird die Therapie durch eine Neck dissection (ND) und/oder adjuvante Radio(chemo)therapie (R(C)T) komplettiert. Ziel war es die onkologischen und funktionellen Ergebnisse sowie das perioperative Management und die postoperativen Komplikationen der primären TLM zur Behandlung von kleinen (T1 - 2), wie auch ausgedehnten (T3 - 4) Pharynxkarzinomen darzustellen.

Obwohl auch im Hypopharynx mit geeigneten Laryngo-pharyngoskopen die transorale Exposition aller Regionen möglich ist (Steiner, 1988; Steiner, 2013), sind zur TLM insbesondere für ausgedehnte Tumoren kaum Kollektive beschrieben. Mit 211 Hypopharynxkarzinom-Patienten haben wir das in der aktuellen Literatur größte und am besten charakterisierte Kollektiv dargestellt (Weiss et al., 2017b). Die 5-Jahres lokale Kontrollrate nach primär TLM (+/- Neck dissection, +/- adjuvanter R(C)T) lag bezogen auf die pT-Kategorie bei 88,1 %, 74,8 %, 77,3 % und 61,8 % für pT1 - 4a Tumoren (Abbildung 1). Die onkologischen Ergebnisse bezogen auf die T-Kategorie und die Tumorstadien zeigt Tabelle 1 (Weiss et al., 2017b). Die guten onkologischen Ergebnisse sind in Einklang mit den Ergebnissen anderer Studien zu TLM bei Hypopharynxkarzinomen (Rudert and Hoft, 2003; Kuo et al., 2013). Unter Berücksichtigung der eingeschränkten Vergleichbarkeit retrospektiver Untersuchungen wurden auch mit offen chirurgischen Verfahren vergleichbare Ergebnisse erzielt (Bova et al., 2005; Kuo et al., 2013), wobei Bova et al. mit der totalen Laryngopharyngektomie mit anschließender Rekonstruktion durch ein Jejunum-Interponat einen deutlich ablativeren Ansatz beschreibt als die organerhaltende TLM. Für diese Kohorte (n = 180, 90 % Stadium III - IVa) mit zu unserem Kollektiv (n = 211, 85 % Stadium III - IVa) vergleichbaren Tumorgrößen und -stadien lag das 5-Jahres Gesamtüberleben bei 33 % (55 % für unsere Kohorte) und das krankheitsspezifische Überleben bei 52 % (74 % für unsere Kohorte) (Bova et al., 2005; Weiss et al., 2017b). Deutlich schlechtere Ergebnisse werden bei fortgeschrittener Erkrankung mittels primärer Radiochemotherapie (RCT) erzielt (bei n = 101, T1 - 4 und 91 % III - IV, 5-Jahres Gesamtüberleben von 18 % und krankheitsspezifisches Überleben 31 %), sodass von den Autoren dieser Studie geschlussfolgert wird, dass primär andere Therapiestrategien berücksichtigt werden sollten (Godballe et al., 2002). Zwar werden mittels primärer RCT bei frühen Erkrankungsstadien (I - II) deutlich bessere Ergebnisse erzielt (Nakamura et al., 2006; Rabbani et al., 2008; Yoshimura et al., 2010), teilt sie dennoch die Toxizität der Hochdosis-Bestrahlung und übertrifft nicht die Ergebnisse der primär chirurgischen Therapiestrategien, wie beispielsweise in unserer Untersuchung dargestellt (Weiss et al., 2017b).

Darüber hinaus wurden durch das von uns dargestellte multimodale Therapiekonzept, das TLM, Neck dissection (88 %) und in vielen Fällen (51 %) auch postoperative R(C)T umfasste gute funktionelle

Ergebnisse erzielt. Wenngleich eine Gastrostomie-Sonde im Zuge der Therapie temporär bei 10 % der Patienten gelegt wurde war diese bei nur 4,3 % dauerhaft erforderlich (Weiss et al., 2017b). Verglichen dazu wird eine Gastrostomie-Sonde im Rahmen der primären RCT routinemäßig gelegt und verbleibt deutlich häufiger für immer (Yao et al., 2006). Auch eine (temporäre) Tracheotomie war nur bei 3,8 % erforderlich (Weiss et al., 2017b).

Ein weiterer Vorteil der TLM scheint die geringe Komplikationsrate zu sein. Am häufigsten kommt es zu Nachblutungen, die in unserem Kollektiv der Hypopharynxkarzinome in 10,4 % der Fälle beobachtet und zumeist mittels transoraler Elektrokoagulation oder *Clipping* versorgt wurden (Weiss et al., 2017b). Dies deckt sich mit den Ergebnissen einer anderen Studie zu TLM bei Hypopharynxkarzinomen (Vilaseca et al., 2004). Auch kam es in unserem Kollektiv in nur zwei Fällen (0,9 %) zu pharyngokutanen Fisteln und in nur einem Fall war eine chirurgische Intervention erforderlich (Weiss et al., 2017b). Dies ist eine deutlich geringere Rate verglichen mit 7,1 % und 10 % Fisteln nach offener Chirurgie (Bova et al., 2005; Kuo et al., 2013).

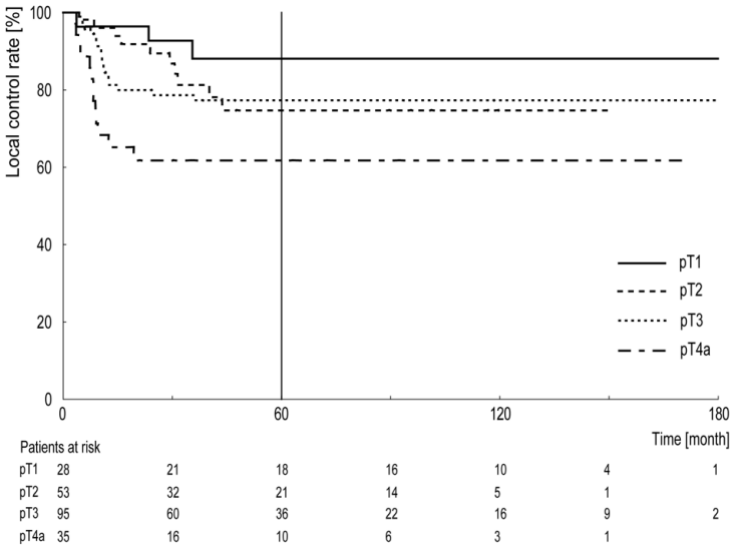

Abbildung 1: 5-Jahres Kaplan-Meier Schätzungen für die lokale Kontrollrate bezogen auf die pT-Kategorie. Anzahl der Patienten unter Risiko unter dem Diagramm dargestellt. (Weiss et al., 2017b)

Tabelle 1. Onkologische Ergebnisse (in Prozent) der primären transoralen Lasermikrochirurgie für 211 Patienten mit Hypopharynxkarzinomen bezogen auf das Tumorstadium und die pT-Kategorie. 5-Jahres Gesamtüberleben (OS), krankheitsspezifische Überleben (DSS), Rezidiv-freie Überleben (RFS), lokale Kontrollrate (LCR). (Weiss et al., 2017b)

	pT1	I-II	pT2	III	pT3	IVa	pT4a	I-IVa	pT1-pT4a
OS	77,6	68,2	52,8	65,9	56,7	44,5	34,0	55,0	55,0
DSS	96,3	96,7	75,4	83,8	76,5	60,7	45,9	74,1	74,1
RFS	77,9	74,6	49,8	56,4	57,8	50,3	40,1	55,9	55,9
LC	88,1		74,8		77,3		61,8		75,7

Auch für Tumoren des Oropharynx stellt die TLM eine Therapieoption dar. Gegenüber der konventionellen Chirurgie, die für umschriebene Tumoren beispielsweise im Bereich der Tonsille oder Gaumenbögen ebenfalls über den transoralen Zugang möglich ist (Laccourreye et al., 2005; Moncrieff et al., 2009), erreicht die TLM unter Verwendung spezieller Zungenspartel, Wundhaken und Laryngo-Pharyngoskope alle Regionen des Oropharynx, insbesondere auch den Zungengrund (Steiner and Ambrosch, 2000; Canis et al., 2013; Steiner, 2013). Darüber hinaus gelten die bereits genannten Vorteile der Laserchirurgie, das geringe Gewebetrauma durch den transoralen Zugang, die blutarmen Operationsbedingungen und die wichtige Eigenschaft unter mikroskopischer Vergrößerung über den Grad der Karbonisierung an der Schnittfläche zwischen Gesunden und befallenem Gewebe zu unterscheiden (Steiner and Ambrosch, 2000). Hierdurch gelingt es auch ausgedehnte Tumoren (T3 - 4a) transoral zu resezieren. Die konventionelle Chirurgie hingegen muss sich hierbei offenen Zugängen wie dem Lipsplit mit Mandibulotomie oder der lateralen Pahryngotomie bedienen (Moncrieff et al., 2009; Rahmati et al., 2015).

In einer retrospektiven Untersuchung haben wir auch für Oropharynxkarzinome die onkologischen und funktionellen Ergebnisse sowie das perioperative Management und die postoperativen Komplikationen der TLM dargestellt. Mit 368 Fällen (pT1 - 4a, pN0 - 2, M0; Stadium I - IVa; 79 % Stadium III/IVa) präsentieren wir die größte Kohorte an chirurgisch und darüber hinaus ausschließlich mittels TLM (+/- ND +/- R(C)T) behandelten Patienten der aktuellen Literatur (Weiss et al., 2019). Die onkologischen Ergebnisse (Tabelle 2) waren im Literaturvergleich mit anderen Untersuchungen zur TLM sowie den konventionellen chirurgischen Verfahren vergleichbar (Laccourreye et al., 2005; Grant et al., 2009; Moncrieff et al., 2009; Rich et al., 2009; Haughey et al., 2011; Iro et al., 2011; Karatzanis et al., 2012; Rahmati et al., 2015).

Wenngleich die Kohorte 79 % fortgeschritten erkrankte (Stadium III/IVa) Oropharynxkarzinom-Patienten mit zu 50 % ausgedehnte T3/4a Tumoren beschreibt waren die funktionellen Ergebnisse des multimodalen Therapiekonzeptes mit primär TLM, Neck dissection (85 %) und in vielen Fällen adjuvante R(C)T (57 %) sehr zufriedenstellend. Insgesamt war die reguläre orale Nahrungszufuhr ohne Abhängigkeit von einer Gastrostomie-Sonde bei 93,5 % möglich. Eine (temporäre) Tracheotomie wurde bei 3,8 % der Patienten angelegt (Weiss et al., 2019).

Eine niedrige Komplikationsrate zeigte sich auch für das Kollektiv der Oropharynxkarzinom-Patienten. Vergleichbar mit der Hypopharynxkarzinom-Kohorte ist mit 11 % die Nachblutung die häufigste Komplikation und ebenfalls selten (1 Fall/0,3 %) wurde eine Fistel beobachtet (Weiss et al., 2017c; Weiss et al., 2019).

Tabelle 2. Onkologische Ergebnisse (in Prozent) der primären transoralen Lasermikrochirurgie für 368 Patienten mit Hypopharynxkarzinomen bezogen auf das Tumorstadium und die pT-Kategorie. 5-Jahres Gesamtüberleben (OS), krankheitsspezifische Überleben (DSS), Rezidiv-freie Überleben (RFS), lokale Kontrollrate (LCR). (Weiss et al., 2019)

	I	pT1	II	pT2	III	pT3	IVa	pT4a	I-IVa	pT1-pT4a
OS	76.0	68.5	71.1	60.0	61.7	62.4	57.3	56.5	61.5	61.5
DSS	92.8	85.1	85.7	74.3	72.5	72.7	73.7	77.0	76.5	76.5
RFS	69.1	67.5	49.6	54.7	58.8	64.8	63.9	61.0	61.3	61.3
LCR	77.7	83.5	63.7	74.1	74.1	77.3	82.0	76.0	77.2	77.2

3.3 Immunhistochemischer p16 Status als prognostischer Faktor bei Oropharynxkarzinomen

Für Oropharynxkarzinome wurde neben den bekannten Risikofaktoren Alkohol- und Tabakabusus (Hashibe et al., 2009) auch eine geographisch unterschiedliche Zunahme einer Assoziation mit HPV-Infektionen beobachtet (D'Souza et al., 2007; Chaturvedi et al., 2011; Gillison et al., 2015; Anantharaman et al., 2017; Wurdemann et al., 2017). Es wurde gezeigt, dass die immunhistochemische Detektion einer diffusen Expression des p16-Proteins mit einer HPV-Infektion korreliert. Folglich wird dies als Surrogatmarker für eine Assoziation des Tumors mit einer onkogenen HPV-Infektion herangezogen (Quabius et al., 2015; Lydiatt et al., 2017).

Wir haben für eine Kohorte von zwischen 2000 und 2015 primär mittels TLM behandelter Oropharynxkarzinom-Patienten (n = 125) nachträglich die p16-Expression immunhistochemisch bestimmt um im Folgenden die onkologischen Ergebnisse zu analysieren. Patienten mit einem p16 positiven Karzinom zeigten im Vergleich zu denen mit einem p16 Negativen ein signifikant höheres Gesamtüberleben und einen klaren Trend zu einem verbesserten krankheitsspezifischen und Rezidiv-freien Überleben (Abbildung 2, Tabelle 3; Weiss et al., 2019). Das unterstützt die Ergebnisse anderer Studien (Rich et al., 2009; Haughey et al., 2011; Rahmati et al., 2015; Park et al., 2017), dass Oropharynxkarzinome mit positivem p16 Status im Vergleich zu p16 negativem eine günstigere Prognose aufweisen (eigene Untersuchung Stadium III/IVa Fälle: Gesamtüberleben: 83 % vs. 63 %, krankheitsspezifisches Überleben: 85 % vs. 71 %, Rezidiv-freie Überleben: 77 % vs. 62 %; Weiss et al., 2019).

Innerhalb der Diskussion zu verschiedenen Behandlungskonzepten berichten die aktuellen Studien über relativ hohe Raten p16 positiver Karzinome oder fokussieren ausschließlich auf den p16 Positiven. Hingegen sind Studien mit einer suffizienten Kohortengröße die exklusiv p16 negative Oropharynxkarzinome definieren und analysieren kaum verfügbar. In unserer Kohorte lag der Anteil

p16 negativer Fälle jedoch bei 56 %, was uns ermöglichte detaillierte Daten nicht nur zu p16 positiven, sondern auch zu explizit p16 negativen Tumoren zu liefern. Demzufolge können wir onkologische Ergebnisse über die größte Gruppe einheitlich therapierter homogen p16 negativer Oropharynxkarzionome demonstrieren, die aktuell in der Literatur verfügbar ist (Weiss et al., 2019).

Zusammenfassend unterstreicht die dargestellte Bedeutung des p16 Status für die Prognose die Notwendigkeit in zukünftigen Untersuchungen zwischen diesen beiden Subgruppen zu differenzieren.

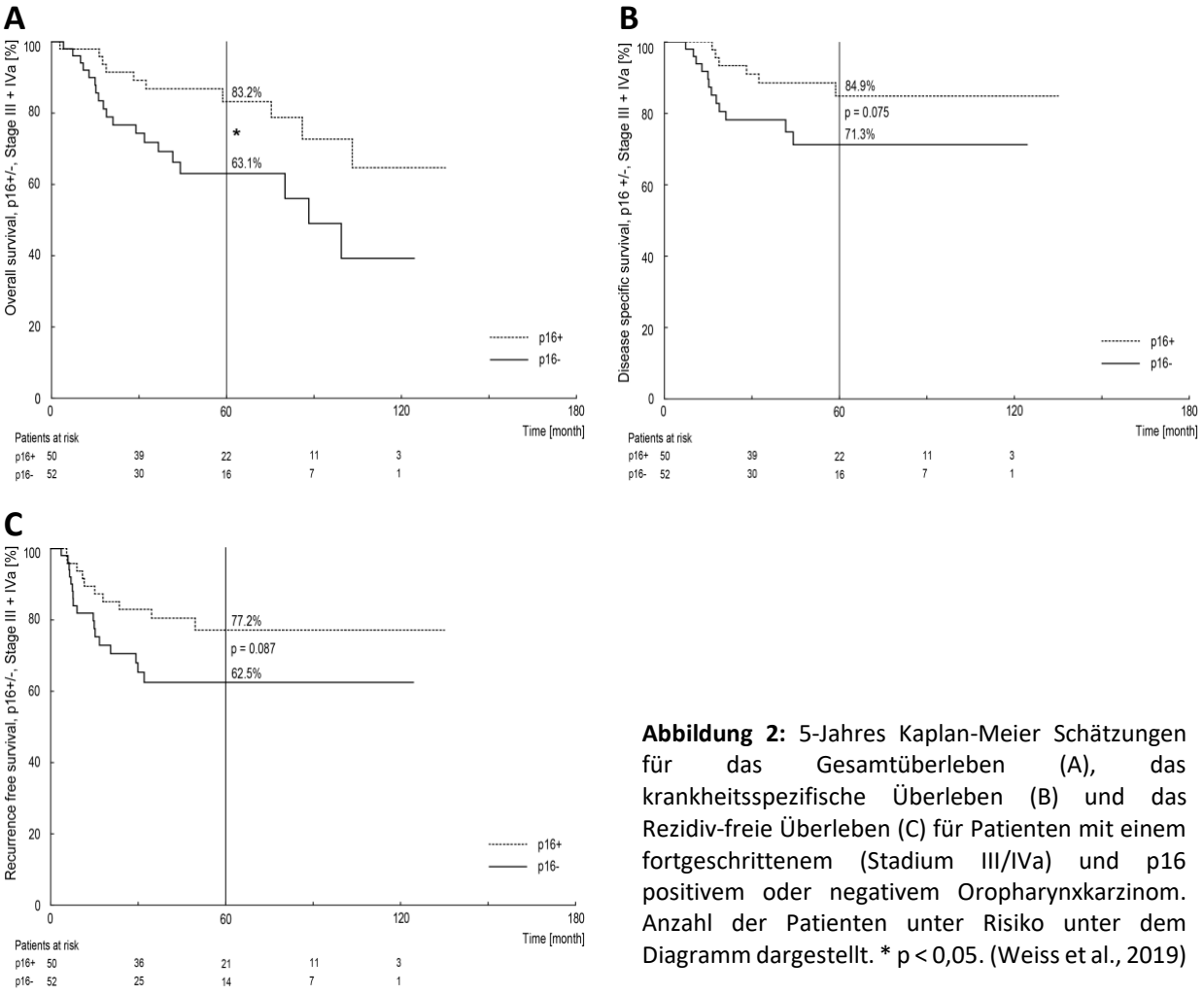

Abbildung 2: 5-Jahres Kaplan-Meier Schätzungen für das Gesamtüberleben (A), das krankheitsspezifische Überleben (B) und das Rezidiv-freie Überleben (C) für Patienten mit einem fortgeschrittenem (Stadium III/IVa) und p16 positivem oder negativem Oropharynxkarzinom. Anzahl der Patienten unter Risiko unter dem Diagramm dargestellt. * $p < 0,05$. (Weiss et al., 2019)

Tabelle 3. Onkologische Ergebnisse (in Prozent) der primären transoralen Lasermikrochirurgie für eine Subgruppe von 102 Patienten mit einem fortgeschrittenem (Stadium III/IVa) und p16 positivem oder negativem Oropharynxkarzinom. 5-Jahres Gesamtüberleben (OS), krankheitsspezifische Überleben (DSS), Rezidiv-freie Überleben (RFS), lokale Kontrollrate (LCR). Signifikante Unterschiede zwischen der Gruppe p16 positiver und p16 negativer Tumore fett gedruckt. (Weiss et al., 2019)

	p16 positiv und negativ (n = 102)	**p16 positiv (n = 50)**	**p16 negativ (n = 52)**	***P* Wert**
OS	73.3	83.2	63.1	**0.019**
DSS	78.3	84.9	71.3	0.075
RFS	69.9	77.2	62.5	0.087
LCR	85.6	89.5	82.4	0.169

3.4 Multimodale Therapie bei fortgeschrittener Tumorerkrankung

Patienten des untersuchten Kollektivs von 579 primär lasermikrochirurgisch behandelten Oro- und Hypopharynxkarzinomen erhielten eine adjuvante Radio(chemo)therapie überwiegend bei fortgeschrittenem Lympknotenbefall (pN2a/b/c) oder wenn die histopathologische Untersuchung extranodales Tumorwachstum und/oder Lymphangiosis carcinomatosa zeigte. Dennoch beinhalteten beide Studien große Kohorten an Patienten mit fortgeschrittener Erkrankung (Stadium III/IVa), die keine adjuvante R(C)T erhielten – nach heutigen Erkenntnissen hätten Sie eine R(C)T erhalten sollen. Daher boten die erhobenen Daten die einmalige Gelegenheit den Einfluss der adjuvanten R(C)T auf das Langzeitüberleben an einer Patientenkohorte zu untersuchen, die aller Voraussicht nach zukünftig nicht mehr zur Verfügung stehen wird. In einer Gruppe von 290 Oropharynxkarzinom-Patienten mit fortgeschrittener Erkrankung hatten jene, die tatsächlich eine adjuvante R(C)T erhielten ein signifikant höheres Rezidiv-freies Überleben sowie eine signifikant höhere lokale Kontrollrate (Abbildung 3; Weiss et al., 2019). Das deckt sich mit den Untersuchungen von Haughey et al., dass eine Radiotherapie nach TLM bei Oropharynxkarzinomen das Risiko eines Rezidivs oder Todes um > 50 % relativ zum nicht-Erhalten dieser adjuvanten Therapie reduziert (Haughey et al., 2011). Auch für die Gruppe von 179 Patienten mit fortgeschrittenem Hypopharynxkarzinom hatten jene, die tatsächlich eine adjuvante R(C)T erhielten signifikant bessere Ergebnisse im Rezidiv-freien Überleben und der lokalen Kontrollrate (Abbildung 4; Weiss et al., 2017c). Zusammenfassend unterstreichen diese Ergebnisse die heutigen Empfehlungen zu einer adjuvanten R(C)T, die sich als wichtige zusätzliche Behandlung bei Karzinomen fortgeschrittenen Stadiums erweist.

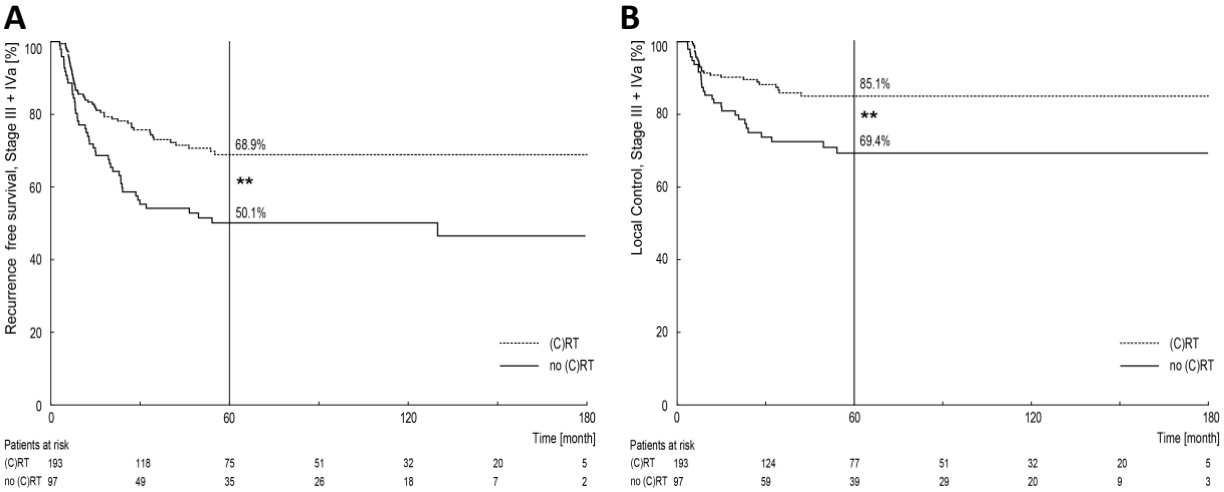

Abbildung 3: 5-Jahres Kaplan-Meier Schätzungen für das Rezidiv-freie Überleben (A) und die lokale Kontrollrate (B) für Patienten mit einem fortgeschrittenem (Stadium III/IVa) Oropharynxkarzinom die nach primärer TLM eine adjuvante Radio(chemo)therapie erhielten [(C)RT] oder diese zusätzliche Therapie nicht erhielten [no (C)RT]. Anzahl der Patienten unter Risiko unter dem Diagramm dargestellt. ** p < 0,01. (Weiss et al., 2019)

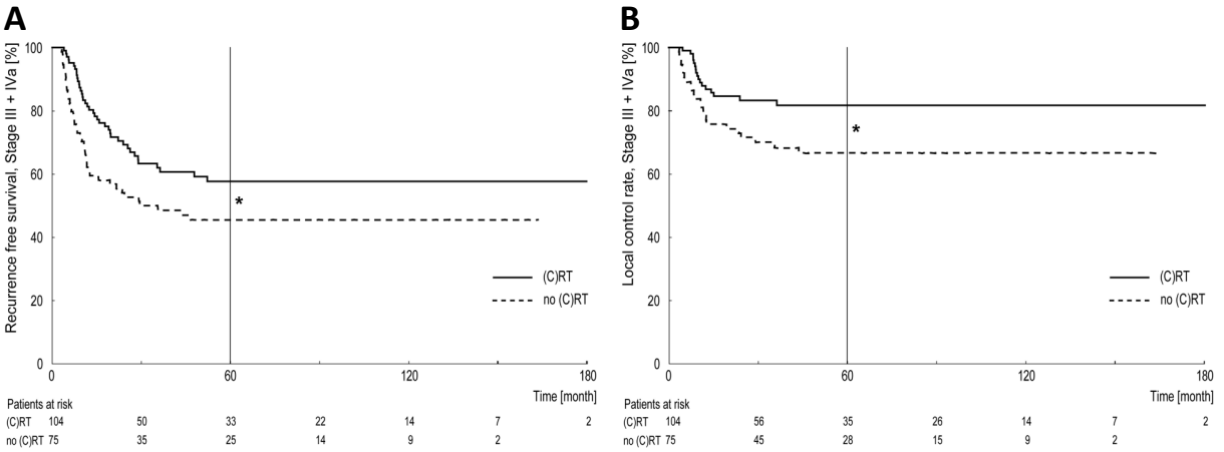

Abbildung 4: 5-Jahres Kaplan-Meier Schätzungen für das Rezidiv-freie Überleben (A) und die lokale Kontrollrate (B) für Patienten mit einem fortgeschrittenem (Stadium III/IVa) Hypopharynxkarzinom die nach primärer TLM eine adjuvante Radio(chemo)therapie erhielten [(C)RT] oder diese zusätzliche Therapie nicht erhielten [no (C)RT]. Anzahl der Patienten unter Risiko unter dem Diagramm dargestellt. * p < 0,05. (Weiss et al., 2017b)

3.5 Transorale Lasermikrochirurgie als Therapieoption bei Tumorrezidiven

Bei Larynxkarzinomen liegt die Rezidivrate bei bis zu 50 % (Goodwin, 2000; Rodrigo et al., 2015). Zur Behandlung stehen auch nach vorausgegangener Radiotherapie chirurgische Therapieoptionen zur Verfügung, wobei diese technisch anspruchsvoll sind und insbesondere Faktoren wie initiale Tumorausdehnung und die vorausgegangenen Behandlungskonzepte berücksichtigt werden müssen (Rodrigo et al., 2015; Ganan et al., 2016). Ungeachtet der immensen funktionellen Einschränkung ist die ablative Laryngektomie ein onkologisch sicherer Therapieansatz in der Rezidivsituation (Rodrigo et al., 2015). Mittels TLM kann neben der Tumorkontrolle auch der Organerhalt ins Therapiekonzept eingebunden werden. Auch TLM ist nach vorausgegangener Radiotherapie möglich (Agra et al., 2012; Ramakrishnan et al., 2014) und aufgrund des transoralen Zugangs sind Komplikationen wie Knorpelnekrosen oder Fisteln unwahrscheinlich (Marioni et al., 2015).

In einer retrospektiven Untersuchung von 199 Patienten mit Rezidiv-Larynxkarzinomen haben wir die Möglichkeit einer erneuten TLM evaluiert. Hierzu wurden Gruppen TLM-behandelter früher (rpT1 - 2, n = 93) und fortgeschrittener (rpT3 - 4a, n = 52) Rezidiv-Larynxkarzinome mit einer Gruppe Laryngektomie-therapierter fortgeschrittener (rpT3 - 4a, n = 54) Tumorrezidive verglichen. Das Gesamt- und krankheitsspezifische Überleben war für die Patienten mit TLM-behandelten frühen Tumoren (64,8 % und 79,6 %) signifikant besser, wobei für fortgeschrittene Tumoren die TLM und Laryngektomie vergleichbare Ergebnisse erzielten (28,9 % und 41,7 % nach TLM; 39,4 % und 44,6 % nach Laryngektomie) (Abbildung 5 A, B) (Weiss et al., 2017a). Der mit einer Laryngektomie einhergehende Funktionsverlust ist jedoch Anreiz organerhaltende chirurgische Konzepte zu verfolgen. Zwar wurde bei den fortgeschrittenen Tumoren durch eine Laryngektomie die höchste lokale Kontrollrate erzielt (Abbildung 5 C) (Weiss et al., 2017a), was auch ein Vergleich zwischen organerhaltender und ablativer Chirurgie aus der Literatur zeigte (Motamed et al., 2006). Ein wichtiger Aspekt ist jedoch, dass in unseren vergleichbaren Patientengruppen, die bei fortgeschrittenen Tumoren mittels TLM oder Laryngektomie behandelt wurden kein Unterschied in den Überlebensraten zu verzeichnen war (Weiss et al., 2017a). Zusammenfassend ist mit dem Ziel des Organerhalts die TLM daher ein valides Konzept auch für fortgeschrittene Tumorrezidive, wobei anatomische und physiologische Faktoren des Patienten, wie auch Einstellbarkeit, Tumorausdehnung und die funktionelle Prognose in die Therapieauswahl mit einfließen müssen. Eine Laryngektomie wird daher immer auch bei einem Anteil an Patienten unter Berücksichtigung aller Faktoren das beste Therapiekonzept bleiben. Für frühe Larynxkarzinomrezidive hingegen halten wir die TLM für das Therapiekonzept der ersten Wahl.

Zudem geht die TLM deutlich seltener mit Komplikationen einher. Beispielsweise werden für die Laryngektomie, insbesondere nach vorausgegangener Radiotherapie Fistelraten von 3 - 21 %

beschrieben (Markou et al., 2004; Paydarfar and Birkmeyer, 2006; Saki et al., 2008; White et al., 2012). In unserem Kollektiv mittels Laryngektomie behandelter Rezidiv-Larynxkarzinome kam es in nur 2 % der Fälle zur Ausbildung einer pharyngokutanen Fistel, die nach konservativer Therapie abheilte (Weiss et al., 2017a). Ist eine operative Behandlung erforderlich kann ein Fibrinogen/Thrombin beschichtetes Kollagen-Vlies als solitäre oder adjuvante Maßnahme für den Verschluss pharyngokutaner Fisteln eingesetzt werden (Weiss et al., 2014).

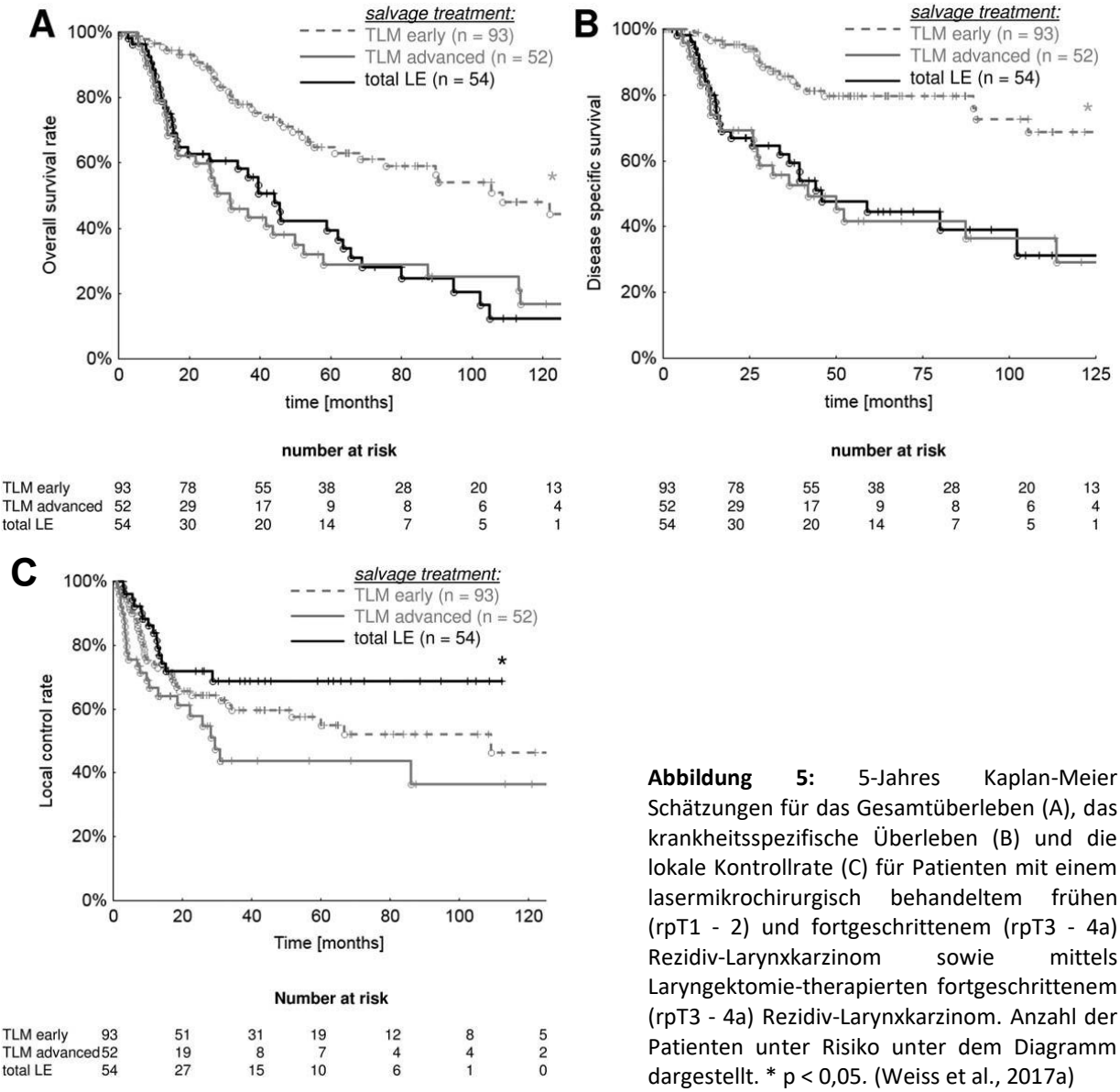

Abbildung 5: 5-Jahres Kaplan-Meier Schätzungen für das Gesamtüberleben (A), das krankheitsspezifische Überleben (B) und die lokale Kontrollrate (C) für Patienten mit einem lasermikrochirurgisch behandeltem frühen (rpT1 - 2) und fortgeschrittenem (rpT3 - 4a) Rezidiv-Larynxkarzinom sowie mittels Laryngektomie-therapierten fortgeschrittenem (rpT3 - 4a) Rezidiv-Larynxkarzinom. Anzahl der Patienten unter Risiko unter dem Diagramm dargestellt. * $p < 0,05$. (Weiss et al., 2017a)

3.6 Rekonstruktionschirurgie und gesundheitsbezogene Lebensqualität

Wenngleich die TLM aufgrund ihres minimalinvasiven Zugangs und der Normalgewebe-schonenden Operationsweise mit sehr zufriedenstellenden onkologischen und funktionellen Ergebnissen einhergeht finden für bestimmte Tumorlokalisationen und bei lokal fortgeschrittenen Tumoren auch rekonstruktionschirurgische Verfahren bei der Evaluation des geeignetsten Behandlungskonzeptes Berücksichtigung. Ziel ist eine Verbesserung von Funktion und damit einhergehend auch der gesundheitsbezogenen Lebensqualität (*health-related quality of life*). Beispielsweise ist nach der Resektion von großen Zungentumoren der Erhalt bzw. die Wiederherstellung der Sprech- und Schluckfunktion eine der wichtigsten Faktoren in Bezug auf eine langfristige Lebensqualität (Pierre et al., 2014). Bei Patienten mit einem Zungenrandkarzinom ist die postoperative Sprech- und Schluckfunktion überwiegend von der Grad des Gewebeverlusts abhängig (Borggreven et al., 2007). Darüber hinaus kann die Narbenbildung die Zunge am Mundboden fixieren und somit die Funktion weiter einschränken (McConnel et al., 1987). Von vielen Autoren wird daher nach partieller Glossektomie für den Mobilitätserhalt der Restzunge eine Weichgewebsrekonstruktion empfohlen (Bokhari and Wang, 2007). Verschiedene freie und gestielte Gewebetransplantate wurden für die Zungenrekonstruktion beschrieben, darunter das freie Radialis- (Urken et al., 1994) und das anterolaterale Oberschenkel-Transplantat (Longo et al., 2013) oder das gestielte supraclavikuläre Inseltransplantat (Chen et al., 2014) und das myocutane Pectoralis major Transplantat (Fang et al., 2013). Andere Autoren hingegen empfehlen eine Rekonstruktion mittels freiem Gewebetransplantat erst nach einer Resektion von mehr als 50 % des Zungenvolumens (Urken et al., 1994). Die Alternative wäre der primäre Wundverschluss (McConnel et al., 1998).

Um dieser Kontroverse zu begegnen haben im Rahmen einer rertrospektiven Untersuchung Patienten mit einem pT3 Zungenrandkarzinom, die nach partieller Glossektomie entweder eine Rekonstruktion mittels freiem Radialistransplantat (n = 20) oder einen primären Wundverschluss (n = 20) erhielten in Bezug auf ihre gesundheitsbezogene Lebensqualität untersucht (Canis et al., 2016). Das durchschnittlich resezierte Zungenvolumen der Rekonstruktions-Gruppe lag bei 41,6 %, das der primären Wundverschluss-Gruppe bei 39.1 %. Alle Patienten wurden primär mittels TLM mit anschließender RCT behandelt, waren zum Zeitpunkt der Erhebung mindestens ein Jahr nach Abschluss der Therapie tumorfrei und hatten Fragebögen zur gesundheitsbezogene Lebensqualität der *European Organization for Research and Treatment of Cancer* (EORCT) bearbeitet (allgemeiner Fragebogen QLQ-C30 Version 3.0 (Aaronson et al., 1993) sowie Kopf-Hals-spezifischer QLQ-H&N35 Version 1.0 (Bjordal et al., 1999)). Es zeigte sich zugunsten der Rekonstruktions-Gruppe ein signifikanter und klinisch relevanter (> 10 Punkte) Unterschied in den Subdomänen Schlucken, Sprechen und Essen im sozialen Kontext des EORCT QLQ-H&N35 Fragebogens (Abbildung 6), was auf

eine verbesserte Funktion nach Rekonstruktion hinweist. Bei allen anderen Items der Fragebögen zeigte sich kein Unterschied (Canis et al., 2016). Die Ergebnisse implizieren, dass eine Rekonstruktion ab einem resezierten Zungenvolumen von 30 - 40 % in Bezug auf Lebensqualität und Funktion von Nutzen sein kann und dass bei geringeren Resektionsvolumina mittels primärem Wundverschluss vergleichbare (oder nach McConnel et al. auch bessere (McConnel et al., 1998)) Ergebnisse erzielt werden könnten.

Das freie mikrovaskulär anastomosierte Radialistransplantat, auch als *Workhorse* für die Rekonstruktion von substanziellen Defekten der Mundhöhle diskutiert (Bokhari and Wang, 2007; Cannady et al., 2014), zeigte sich auch in unserer Arbeit zur Rekonstruktion nach partieller Glossektomie geeignet (Canis et al., 2016). Seine Eigenschaften als dünnes Transplantat mit konstanter Anatomie, biegsam und in Größe und Form variabel könnte es mit dem supraclavikulären Inseltransplantat (SCAIF) teilen. Das supraclavikuläre Inseltransplantat könnte zudem den Vorteil der stabilen Blutversorgung eines gestielten Gewebetransplantas wie dem myocutane Pectoralis major Transplantat mit der Flexibilität des dünnen Radialistransplantats kombinieren.

Wir haben zwei homogene Gruppen von jeweils 25 Patienten die nach Tumorresektion eines fortgeschrittenen Plattenepithelkarzinoms der Mundhöhle oder des Oropharynx entweder mittels freiem Radialistransplantat oder gestieltem SCAIF rekonstruiert wurden verglichen (Welz et al., 2017). Es zeigte sich kein Unterschied bei peri- und postoperativen Komplikationen und der anschließenden Fähigkeit zur oralen Nahrungsaufnahme. Die Operationszeit war bei der Gruppe SCAIF-rekonstruierter Patienten signifikant geringer, was auf eine kürzere Hebedauer und die wegfallende mikrovaskuläre Anastomose beim SCAIF zurückzuführen war. Auch waren in dieser Gruppe weniger Tracheotomien (prophylaktisch bei erwarteter Schwellung und/oder als Aspirationsschutz) oder postoperative Intensivstationsaufenthalte (meist prophylaktisch u. a. zum intensiveren Monitoring der Transplantatvitalität) erforderlich (Welz et al., 2017). Zusammenfassend scheint der SCAIF ein dem Radialistransplantat vergleichbares und verlässliches Transplantat zur Rekonstruktion von Defekten der Mundhöhle und des Oropharynx zu sein.

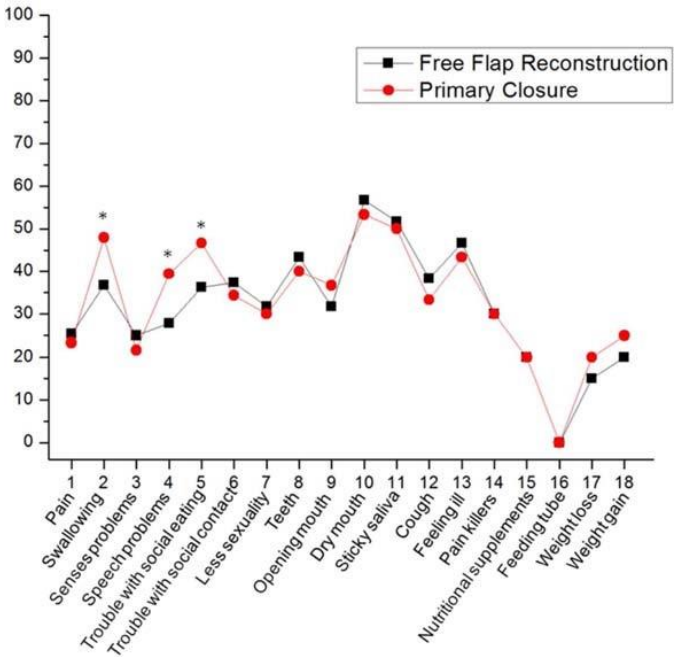

Abbildung 6: Mittelwerte der Items des Kopf-Hals-spezifischen Fragebogens zur gesundheitsbezogene Lebensqualität der *European Organization for Research and Treatment of Cancer* (EORCT QLQ-H&N35) von Patienten nach partieller Glossektomie und Rekonstruktion mittels Radialistransplantat (schwarze Kurve) oder primären Wundverschluss (rote Kurve). Zugunsten der Rekonstruktions-Gruppe zeigt sich ein signifikanter und klinisch relevanter (> 10 Punkte) Unterschied in den Subdomänen Schlucken, Sprechen und Essen im sozialen Kontext. * $p < 0,05$. (Canis et al., 2016)

3.7 Histopathologische Bestätigung der vollständigen Tumorresektion (R0)

Ein ausreichend im Gesunden resezierter Tumor ist das Ziel der kurativen Tumortherapie. Hierbei ist der Standard der chirurgischen Onkologie die en bloc Resektion. Aufgrund anatomischer Beschränkungen (beispielsweise an der mittleren oder lateralen Schädelbasis) oder funktionellen Ansprüchen an die chirurgische Therapie (z. B. erhalt der Schluckfunktion oder Stimme) kann jedoch auch eine Stück für Stück (*piece-meal*) Resektion gerechtfertigt sein (Steiner, 1993; Wellman et al., 1999). Bei der minimalinvasiven transoralen Lasermikrochirurgie wird hierbei der Tumor nicht nur aufgrund des eingeschränkten Zugangsweges in Stücke zerlegt, sondern auch um mittels Schnitt durch den Tumor unter mikroskopischer Sicht bereits intraoperativ die Tumorgrenzen bzw. Tiefenausdehnung zu evaluieren und somit gesundes Gewebe maximal zu schonen (Steiner, 1988; Steiner and Ambrosch, 2000; Steiner, 2013). Die enge Zusammenarbeit mit den Pathologen ist hierbei jedoch essentiell um an Randproben mittels Gefrierschnittuntersuchung die Tumorfreiheit der Resektionsränder mikroskopisch bestätigen zu lassen. Wobei sich auch hierbei das Team der methodischen Einschränkungen bewusst sein muss. Für die Gefrierschnittuntersuchung bei Kopf-Hals-Plattenepithelkarzinomen wurden Raten fehlender Übereinstimmung zwischen Schnellschnittergebnis und endgültigem Befund von 3,1 % beobachtet. Die Sensitivität und Spezifität lag bei 89 % und 98 % (Layfield et al., 2018). Gegebenenfalls sollten folglich Nachresektionen in Erwägung gezogen werden. Zu berücksichtigen ist jedoch auch, dass selbst die Methode der Gewinnung von Randproben Einfluss auf die onkologischen Ergebnisse haben könnte. In Kollaboration mit Kollegen des Instituts für

Pathologie der Universität Pittsburgh, Pennsylvania sowie vier weiteren Kopf-Hals-chirurgischen Kliniken in den USA und Canada haben wir an einem Kollektiv von 280 Patienten mit einem pT1 - 2 pN0 Plattenepithelkarzinom der Zunge Methoden der Randprobengewinnung evaluiert. Erfolgte die Randprobengewinnung zur Bestätigung tumorfreier Resektionsränder ausschließlich vom Tumorresektat/Hauptpräparat war das 3-Jahres-Lokalrezidiv-freie Überleben im Vergleich zur Randprobengewinnung aus dem Tumorbett signifikant höher (90 % vs. 80 %). Auch war bei der Probengewinnung aus dem Tumorbett im Durchschnitt ein knapperer Resektionsrand festzustellen (Maxwell et al., 2015). Folglich sollte bei Möglichkeit die Evaluation des Randstatus am Hauptpräparat bestätigt werden. Hierbei unterstütz die Einsendung markierter Tumorresektate sowie der enge Austausch mit den Pathologen den Beurteilungsprozess. In der auf Organerhalt und Gewebeschonung abzielenden TLM bleibt jedoch oft aufgrund der Größe und Anzahl der Resektate eine sorgfältige Gewinnung und Untersuchung von Randschnitten aus dem Tumorbett die Methode der Wahl. Gegenüber konventionell chirurgischen Verfahren, bei denen eine en bloc Resektion leichter zu erzielen ist, haben dennoch eine Vielzahl auch eigener Untersuchungen von großen und primär TLM-behandelten Kollektiven wenigstens vergleichbar gute onkologische Ergebnisse darstellen können (Rich et al., 2009; Haughey et al., 2011; Canis et al., 2014a; Canis et al., 2014b; Canis et al., 2014c; Weiss et al., 2017c; Weiss et al., 2017b). Zudem ist eine Nachresektion nach TLM zumeist uneingeschränkt möglich und auch im Vergleich mit bereits im ersten Schritt mittels TLM R0-resezierter Tumoren nicht mit einer schlechteren lokoregionären Kontrolle verbunden (Jackel et al., 2007). Darüber hinaus geben engmaschige Nachsorgeuntersuchungen und bei endoskopisch schwer zu beurteilenden Primärlokalisationen auch eine mikrolaryngoskopische Bestandsaufnahme (in Vollnarkose einige Wochen nach Abschluss der primären Tumortherapie, *second-look* Mikrolaryngoskopie) weitere onkologische Sicherheit (Preuss et al., 2009).

Auch bei Tumoren der lateralen Schädelbasis erfolgt die Resektion schrittweise mit anschließender histopathologischer Beurteilung von Randschnitten aus dem Tumorbett. In einer weiteren Multizenterstudie haben wir die onkologische Behandlung und den Einfluss des chirurgisch erzielten Resektionsrandes der sehr seltenen und mit einer schlechten Prognose einhergehenden Gehörgangskarzinome untersucht (Ihler et al., 2015). Aufgrund funktioneller Erwägungen, wie dem Versuch den Nervus facialis und die Mittel- oder Innenohrstrukturen zu schonen wurde bei einem hohen Anteil von 56 % der Patienten kein tumorfreier Resektionsrand erzielt. Ungeachtet der R1-Situation führte das Gesamtkonzept der Kombination aus chirurgischer Behandlung und adjuvanter Radiochemotherapie zu einem vergleichbaren 5-Jahres Gesamtüberleben (56,6 %) wie diese Behandlung bei R0-Resektion (59,4 %). Ein signifikant schlechteres Gesamtüberleben war bei nicht-resektablen und primär radiochemotherapierten Fällen zu beobachten (Abbildung 7) (Ihler et al.,

2015). Dies ist übereinstimmend mit Untersuchungen anderer, die nach alleiniger RCT bei fortgeschrittenen Gehörgangskarzinomen ein 5-Jahres Gesamtüberleben von 28,7 % beobachteten (Zhang et al., 1999). Auch zeigte sich in unserer Untersuchung die lokale Kontrollrate mit 26,3 % bei R1-Status trotz zumeist erfolgter adjuvanter RCT gegenüber 74,2 % nach R0-Resektion deutlich geringer (Ihler et al., 2015), was den Wert der anzustrebenden vollständigen chirurgischen Tumorkontrolle weiter unterstreicht.

Zusammenfassend ist für eine erfolgreiche Tumortherapie die Schnittstelle zwischen Chirurgie und Pathologie von immenser Bedeutung, an ihr hängt die korrekte Diagnosestellung, die optimale chirurgische Tumorkontrolle, wie auch die konsensuelle Entscheidungsfindung zur adjuvanten Therapie.

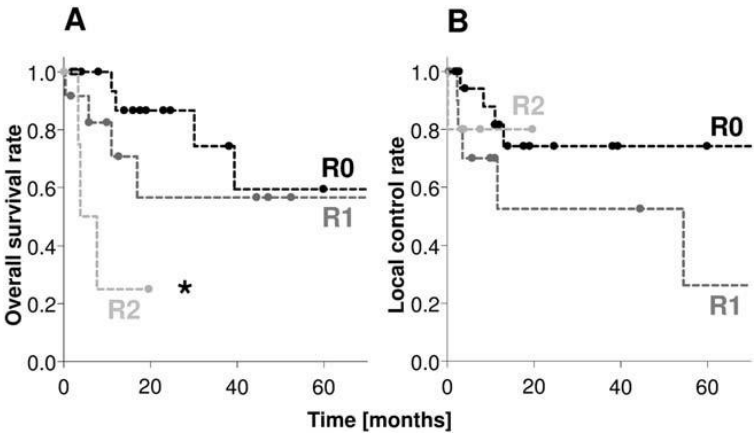

Abbildung 7: 5-Jahres Kaplan-Meier Schätzungen für das Gesamtüberleben (A) und lokale Kontrollrate (B) bezogen auf den Resektionsstatus. * p = 0,010 (R0 vs. R2). R0 = histologisch gesicherter freier Resektionsrand; R1 = makros-kopisch aber nicht mikroskopisch freier Resektionsrand; R2 = Biopsie oder abgebrochene chirurgische Therapie mit makroskopischem Residualtumor). (Ihler et al., 2015)

4 Zusammenfassung

Die vorliegende Habilitationsarbeit befasst sich mit der transoralen Lasermikrochirurgie zur Behandlung von Kopf-Hals-Malignomen im Gesamtkonzept multimodaler Therapiestrategien. Hierzu wurden nicht nur die hervorragenden onkologischen und funktionellen Ergebnisse sowie die geringe Komplikationsrate der TLM für frühe wie auch fortgeschrittene Tumoren des Larynx und Pharynx dargestellt, sondern insbesondere auch der Wert einer adjuvanten Radio(chemo)therapie im Falle fortgeschrittener Erkrankungen demonstriert.

Die bei Oropharynxkarzinomen dargestellte Bedeutung des p16 Status unterstreicht die Notwendigkeit in zukünftigen Untersuchungen zwischen den beiden Subgruppen des p16 positiven und negativen Tumors zu differenzieren.

Im Falle eines Tumorrezidivs erlauben unsere Untersuchungen zu Larynxkarzinomen den Schluss, dass eine erneute TLM als Therapieoption der ersten Wahl für lokal umschriebene Tumorrezidive und mit dem Ziel des Organerhalts unter strenger Indikationsstellung als Alternative zur Laryngektomie auch für lokal fortgeschrittene Rezidive in Erwägung gezogen werden kann.

Die TLM und die auf konventionell-offen chirurgischen Verfahren basierende Rekonstruktionschirurgie schließen sich keineswegs aus. Wir haben für Patienten mit pT3 Zungenrandkarzinomen, bei denen nach TLM der Defekt entweder primär verschlossen oder mittels Radialistransplantat rekonstruiert wurde eine Überlegenheit in Parametern zur gesundheitsbezogenen Lebensqualität zugunsten der Rekonstruktion dargestellt. In einer weiteren Untersuchung haben wir die Eignung des supraclavikulären Insentransplantas zur Rekonstruktion von Resektionsdefekten im Bereich der Mundhöhle und des Oropharynx im Vergleich zum etablierten Radialistransplantat dargestellt.

Behandlungsstrategien von Kopf-Hals-Malignomen sollten nicht nur in interdisziplinären Konferenzen diskutiert und im Konsens entschieden, sondern stets auch unter interdisziplinären Gesichtspunkten reevaluiert werden. Um Fragestellungen unterschiedlicher Blickwinkel zu adressieren hat sich die wissenschaftliche Zusammenarbeit mit Kolleginnen und Kollegen der Strahlentherapie und Radioonkologie, der Pathologie, der Radiologie und der medizinischen Onkologie auch im Rahmen der vorliegenden Habilitationsarbeit bewährt. Mehr prospektive randomisierte Studien sind erforderlich um unterschiedliche Therapiestrategien zu Kopf-Hals-Malignomen unter Berücksichtigung onkologischer und funktioneller Ergebnisse, wie auch gesundheitsbezogener Lebensqualität und tumorbiologischer Aspekte zu vergleichen. Hierin soll ein Schwerpunkt meiner zukünftigen wissenschaftlichen Tätigkeit liegen.

Entsprechend des Schriftenverzeichnisses wurden im Rahmen der vorgestellten wissenschaftlichen Tätigkeit von mir bisher 24 Originalarbeiten veröffentlicht, davon 7 als Erst- und eine als geteilter Letztautor. Mit Erstautorschaft wurden zudem eine Kasuistik, zwei Übersichtsartikel und eine Patentanmeldung veröffentlicht.

5 Literaturverzeichnis

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 85:365-376.

Agra IM, Ferlito A, Takes RP, Silver CE, Olsen KD, Stoeckli SJ, Strojan P, Rodrigo JP, Goncalves Filho J, Genden EM, Haigentz M, Jr., Khafif A, Weber RS, Zbaren P, Suarez C, Hartl DM, Rinaldo A, Kim KH, Kowalski LP (2012) Diagnosis and treatment of recurrent laryngeal cancer following initial nonsurgical therapy. Head Neck 34:727-735.

Altuna X, Zulueta A, Algaba J (2005) CO2 laser cordectomy as a day-case procedure. J Laryngol Otol 119:770-773.

Anantharaman D et al. (2017) Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. International journal of cancer Journal international du cancer 140:1968-1975.

Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, Garden AS, Shenouda G, Harris J, Ang KK (2014) Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. International journal of radiation oncology, biology, physics 89:13-20.

Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, Biorklund A, de Leeuw JR, Fayers PM, Jannert M, Westin T, Kaasa S (1999) Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 17:1008-1019.

Bokhari WA, Wang SJ (2007) Tongue reconstruction: recent advances. Curr Opin Otolaryngol Head Neck Surg 15:202-207.

Borggreven PA, Aaronson NK, Verdonck-de Leeuw IM, Muller MJ, Heiligers ML, Bree R, Langendijk JA, Leemans CR (2007) Quality of life after surgical treatment for oral and oropharyngeal cancer: a prospective longitudinal assessment of patients reconstructed by a microvascular flap. Oral Oncol 43:1034-1042.

Bourhis J et al. (2012) Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol 13:145-153.

Bova R, Goh R, Poulson M, Coman WB (2005) Total pharyngolaryngectomy for squamous cell carcinoma of the hypopharynx: a review. Laryngoscope 115:864-869.

Canis M, Ihler F, Martin A, Matthias C, Steiner W (2014a) Transoral laser microsurgery for T1a glottic cancer: Review of 404 cases. Head Neck.

Canis M, Ihler F, Wolff HA, Christiansen H, Matthias C, Steiner W (2013) Oncologic and functional results after transoral laser microsurgery of tongue base carcinoma. Eur Arch Otorhinolaryngol 270:1075-1083.

Canis M, Ihler F, Martin A, Wolff HA, Matthias C, Steiner W (2014b) Enoral laser microsurgery for squamous cell carcinoma of the oral cavity. Head Neck 36:787-794.

Canis M, Weiss BG, Ihler F, Hummers-Pradier E, Matthias C, Wolff HA (2016) Quality of life in patients after resection of pT3 lateral tongue carcinoma: Microvascular reconstruction versus primary closure. Head Neck 38:89-94.

Canis M, Martin A, Ihler F, Wolff HA, Kron M, Matthias C, Steiner W (2014c) Transoral laser microsurgery in treatment of pT2 and pT3 glottic laryngeal squamous cell carcinoma - results of 391 patients. Head Neck 36:859-866.

Cannady SB, Rosenthal EL, Knott PD, Fritz M, Wax MK (2014) Free tissue transfer for head and neck reconstruction: a contemporary review. JAMA Facial Plast Surg 16:367-373.

Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML (2011) Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29:4294-4301.

Chen WL, Zhang DM, Yang ZH, Wang YY, Fan S (2014) Functional hemitongue reconstruction using innervated supraclavicular fasciocutaneous island flaps with the cervical plexus and reinnervated supraclavicular fasciocutaneous island flaps with neurorrhaphy of the cervical plexus and lingual nerve. Head Neck 36:66-70.

D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML (2007) Case-control study of human papillomavirus and oropharyngeal cancer. The New England journal of medicine 356:1944-1956.

Dinapoli N, Parrilla C, Galli J, Autorino R, Micciche F, Bussu F, Balducci M, D'Alatri L, Marchese R, Rigante M, Di Lella G, Liberati L, Almadori G, Paludetti G, Valentini V (2010) Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al] 186:607-613.

Edge SB, Compton CC (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17:1471-1474.

Fang QG, Shi S, Zhang X, Li ZN, Liu FY, Sun CF (2013) Assessment of the quality of life of patients with oral cancer after pectoralis major myocutaneous flap reconstruction with a focus on speech. J Oral Maxillofac Surg 71:2004 e2001-2004 e2005.

Ganan L, Lopez M, Garcia J, Esteller E, Quer M, Leon X (2016) Management of recurrent head and neck cancer: variables related to salvage surgery. Eur Arch Otorhinolaryngol 273:4417-4424.

Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C (2015) Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33:3235-3242.

Godballe C, Jorgensen K, Hansen O, Bastholt L (2002) Hypopharyngeal cancer: results of treatment based on radiation therapy and salvage surgery. Laryngoscope 112:834-838.

Goodwin WJ, Jr. (2000) Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 110:1-18.

Grant DG, Hinni ML, Salassa JR, Perry WC, Hayden RE, Casler JD (2009) Oropharyngeal cancer: a case for single modality treatment with transoral laser microsurgery. Arch Otolaryngol Head Neck Surg 135:1225-1230.

Hashibe M et al. (2009) Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 18:541-550.

Haughey BH, Hinni ML, Salassa JR, Hayden RE, Grant DG, Rich JT, Milov S, Lewis JS, Jr., Krishna M (2011) Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. Head Neck 33:1683-1694.

Hirasawa N, Itoh Y, Naganawa S, Ishihara S, Suzuki K, Koyama K, Murao T, Asano A, Nomoto Y, Horikawa Y, Sasaoka M, Obata Y (2012) Multi-institutional analysis of early glottic cancer from 2000 to 2005. Radiation oncology 7:122.

Ihler F, Koopmann M, Weiss BG, Droge LH, Durisin M, Christiansen H, Weiss D, Canis M, Wolff HA (2015) Surgical margins and oncologic results after carcinoma of the external auditory canal. Laryngoscope 125:2107-2112.

Iro H, Mantsopoulos K, Zenk J, Waldfahrer F, Psychogios G (2011) [Results of transoral laser resection in T1-2 oropharyngeal, hypopharyngeal and laryngeal carcinomas]. Laryngorhinootologie 90:481-485.

Jackel MC, Ambrosch P, Martin A, Steiner W (2007) Impact of re-resection for inadequate margins on the prognosis of upper aerodigestive tract cancer treated by laser microsurgery. Laryngoscope 117:350-356.

Karatzanis AD, Psychogios G, Waldfahrer F, Zenk J, Velegrakis GA, Iro H (2012) Surgical management of T1 oropharyngeal carcinoma. Head Neck 34:1277-1282.

Karatzanis AD, Psychogios G, Zenk J, Waldfahrer F, Hornung J, Velegrakis GA, Iro H (2009) Comparison among different available surgical approaches in T1 glottic cancer. Laryngoscope 119:1704-1708.

Kuo CL, Lee TL, Chu PY (2013) Conservation surgery for hypopharyngeal cancer: changing paradigm from open to endoscopic. Acta Otolaryngol 133:1096-1103.

Laccourreye O, Hans S, Menard M, Garcia D, Brasnu D, Holsinger FC (2005) Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. Arch Otolaryngol Head Neck Surg 131:592-599.

Layfield EM, Schmidt RL, Esebua M, Layfield LJ (2018) Frozen Section Evaluation of Margin Status in Primary Squamous Cell Carcinomas of the Head and Neck: A Correlation Study of Frozen Section and Final Diagnoses. Head and neck pathology 12:175-180.

Lei WB, Jiang AY, Chai LP, Zhu XL, Wang ZF, Wen YH, Su ZZ, Wen WP (2013) Middle frontal horizontal partial laryngectomy (MFHPL): a treatment for stage T1b squamous cell carcinoma of the glottic larynx involving anterior vocal commissure. PLoS One 8:e52723.

Longo B, Ferri G, Fiorillo A, Rubino C, Santanelli F (2013) Bilobed perforator free flaps for combined hemitongue and floor-of-the-mouth defects. Journal of plastic, reconstructive & aesthetic surgery : JPRAS 66:1464-1469.

Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, Loomis AM, Shah JP (2017) Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 67:122-137.

Marioni G, Marchese-Ragona R, Kleinsasser NH, Lionello M, Lawson G, Hagen R, Staffieri A (2015) Partial laryngeal surgery in recurrent carcinoma. Acta Otolaryngol 135:119-124.

Markou K, Nikolaou A, Nalbadian M, Petridis D, Nicolaidis V, Daniilidis I (2002) How often is total laryngectomy necessary for the treatment of T1 failures after radiotherapy or cordectomy? Eur Arch Otorhinolaryngol 259:4-10.

Markou KD, Vlachtsis KC, Nikolaou AC, Petridis DG, Kouloulas AI, Daniilidis IC (2004) Incidence and predisposing factors of pharyngocutaneous fistula formation after total laryngectomy. Is there a relationship with tumor recurrence? Eur Arch Otorhinolaryngol 261:61-67.

Maxwell JH, Thompson LD, Brandwein-Gensler MS, Weiss BG, Canis M, Purgina B, Prabhu AV, Lai C, Shuai Y, Carroll WR, Morlandt A, Duvvuri U, Kim S, Johnson JT, Ferris RL, Seethala R, Chiosea SI (2015) Early Oral Tongue Squamous Cell Carcinoma: Sampling of Margins From Tumor Bed and Worse Local Control. JAMA Otolaryngol Head Neck Surg 141:1104-1110.

McConnel FM, Teichgraeber JF, Adler RK (1987) A comparison of three methods of oral reconstruction. Arch Otolaryngol Head Neck Surg 113:496-500.

McConnel FM, Pauloski BR, Logemann JA, Rademaker AW, Colangelo L, Shedd D, Carroll W, Lewin J, Johnson J (1998) Functional results of primary closure vs flaps in oropharyngeal reconstruction: a prospective study of speech and swallowing. Arch Otolaryngol Head Neck Surg 124:625-630.

Moncrieff M, Sandilla J, Clark J, Clifford A, Shannon K, Gao K, O'Brien C (2009) Outcomes of primary surgical treatment of T1 and T2 carcinomas of the oropharynx. Laryngoscope 119:307-311.

Motamed M, Laccourreye O, Bradley PJ (2006) Salvage conservation laryngeal surgery after irradiation failure for early laryngeal cancer. Laryngoscope 116:451-455.

Nakamura K, Shioyama Y, Kawashima M, Saito Y, Nakamura N, Nakata K, Hareyama M, Takada T, Karasawa K, Watanabe T, Yorozu A, Tachibana H, Suzuki G, Hayabuchi N, Toba T, Yamada S (2006) Multi-institutional analysis of early squamous cell carcinoma of the hypopharynx treated with radical radiotherapy. International journal of radiation oncology, biology, physics 65:1045-1050.

Park YM, Kim HR, Cho BC, Keum KC, Cho NH, Kim SH (2017) Transoral robotic surgery-based therapy in patients with stage III-IV oropharyngeal squamous cell carcinoma. Oral Oncol 75:16-21.

Paydarfar JA, Birkmeyer NJ (2006) Complications in head and neck surgery: a meta-analysis of postlaryngectomy pharyngocutaneous fistula. Arch Otolaryngol Head Neck Surg 132:67-72.

Pierre CS, Dassonville O, Chamorey E, Poissonnet G, Ettaiche M, Santini J, Peyrade F, Benezery K, Sudaka A, Bozec A (2014) Long-term quality of life and its predictive factors after oncologic surgery and microvascular reconstruction in patients with oral or oropharyngeal cancer. Eur Arch Otorhinolaryngol 271:801-807.

Pignataro L, Capaccio P, Neglia CB, Ottaviani A (2000) Clinical experience with the treatment of T1b glottic cancer by means of horizontal glottectomy. Eur Arch Otorhinolaryngol 257:216-218.

Preuss SF, Cramer K, Drebber U, Klussmann JP, Eckel HE, Guntinas-Lichius O (2009) Second-look microlaryngoscopy to detect residual carcinoma in patients after laser surgery for T1 and T2 laryngeal cancer. Acta Otolaryngol 129:881-885.

Quabius ES, Haag J, Kuhnel A, Henry H, Hoffmann AS, Gorogh T, Hedderich J, Evert M, Beule AG, Maune S, Knecht R, Ovari A, Durisin M, Hoppe F, Tribius S, Rocken C, Ambrosch P, Hoffmann M (2015)

Geographical and anatomical influences on human papillomavirus prevalence diversity in head and neck squamous cell carcinoma in Germany. Int J Oncol 46:414-422.

Rabbani A, Amdur RJ, Mancuso AA, Werning JW, Kirwan J, Morris CG, Mendenhall WM (2008) Definitive radiotherapy for T1-T2 squamous cell carcinoma of pyriform sinus. International journal of radiation oncology, biology, physics 72:351-355.

Rahmati R, Dogan S, Pyke O, Palmer F, Awad M, Lee N, Kraus DH, Shah JP, Patel SG, Ganly I (2015) Squamous cell carcinoma of the tonsil managed by conventional surgery and postoperative radiation. Head Neck 37:800-807.

Ramakrishnan Y, Drinnan M, Kwong FN, Grant DG, Mehanna H, Jones T, Paleri V (2014) Oncologic outcomes of transoral laser microsurgery for radiorecurrent laryngeal carcinoma: a systematic review and meta-analysis of English-language literature. Head Neck 36:280-285.

Rich JT, Milov S, Lewis JS, Jr., Thorstad WL, Adkins DR, Haughey BH (2009) Transoral laser microsurgery (TLM) +/- adjuvant therapy for advanced stage oropharyngeal cancer: outcomes and prognostic factors. Laryngoscope 119:1709-1719.

Robert-Koch-Institut (2017) Krebs in Deutschland für 2013/2014, 11. Ausgabe Edition: Robert Koch-Institut (Hrsg) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg).

Rodrigo JP, Kowalski LP, Silver CE, de Bree R, Rinaldo A, Shaha AR, Strojan P, Elsheikh MN, Haigentz M, Jr., Sanabria A, Coskun HH, Takes RP, Ferlito A (2015) When is reoperative surgery not indicated for recurrent head and neck squamous cell carcinoma? Eur Arch Otorhinolaryngol 272:259-262.

Rudert HH, Hoft S (2003) Transoral carbon-dioxide laser resection of hypopharyngeal carcinoma. Eur Arch Otorhinolaryngol 260:198-206.

Saki N, Nikakhlagh S, Kazemi M (2008) Pharyngocutaneous fistula after laryngectomy: incidence, predisposing factors, and outcome. Arch Iran Med 11:314-317.

Sobin LH, Compton CC (2010) TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer 116:5336-5339.

Steiner W (1988) Experience in endoscopic laser surgery of malignant tumours of the upper aero-digestive tract. Advances in oto-rhino-laryngology 39:135-144.

Steiner W (1993) Results of curative laser microsurgery of laryngeal carcinomas. Am J Otolaryngol 14:116-121.

Steiner W, Ambrosch P (2000) Endoscopic laser surgery of the upper aerodigestive tract with special emphasis on cancer sugery. Stuttgart: New York : Thieme.

Steiner WH, David; Haughey, Bruce; Bernal-Sprekelsen, Manuel (2013) Transoral Laser Microsurgery for Cancer of the Upper Aerodigestive Tract. Tuttlingen, Germany: Endo-Press.

Strong MS, Jako GJ (1972) Laser surgery in the larynx. Early clinical experience with continuous CO 2 laser. Ann Otol Rhinol Laryngol 81:791-798.

Urken ML, Moscoso JF, Lawson W, Biller HF (1994) A systematic approach to functional reconstruction of the oral cavity following partial and total glossectomy. Arch Otolaryngol Head Neck Surg 120:589-601.

Vilaseca I, Blanch JL, Bernal-Sprekelsen M, Moragas M (2004) CO2 laser surgery: a larynx preservation alternative for selected hypopharyngeal carcinomas. Head Neck 26:953-959.

Warner L, Chudasama J, Kelly CG, Loughran S, McKenzie K, Wight R, Dey P (2014) Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. Cochrane Database Syst Rev 12:CD002027.

Weiss BG, Ihler F, Matthias C, Canis M (2014) Coated collagen patches for closure of pharyngo-cutaneous fistulas. Am J Otolaryngol 35:246-250.

Weiss BG, Bertlich M, Canis M, Ihler F (2017a) Transoral laser microsurgery or total laryngectomy for recurrent squamous cell carcinoma of the larynx: Retrospective analysis of 199 cases. Head Neck 39:1166-1176.

Weiss BG, Ihler F, Wolff HA, Schneider S, Canis M, Steiner W, Welz C (2017b) Transoral laser microsurgery for treatment for hypopharyngeal cancer in 211 patients. Head Neck 39:1631-1638.

Weiss BG, Ihler F, Pilavakis Y, Wolff HA, Canis M, Welz C, Steiner W (2017c) Transoral laser microsurgery for T1b glottic cancer: review of 51 cases. Eur Arch Otorhinolaryngol 274:1997-2004.

Weiss BG, Ihler F, Anczykowski MZ, Bertlich M, Kitz J, Steiner W, Canis M, Jakob M (2019) Transoral laser microsurgery for treatment of oropharyngeal cancer in 368 patients. Head Neck 41:3144-3158.

Wellman BJ, Traynelis VC, McCulloch TM, Funk GF, Menezes AH, Hoffman HT (1999) Midline anterior craniofacial approach for malignancy: results of en bloc versus piecemeal resections. Skull Base Surg 9:41-46.

Welz C, Canis M, Schwenk-Zieger S, Spiegel JL, Weiss BG, Pilavakis Y (2017) Oral Cancer Reconstruction Using the Supraclavicular Artery Island Flap: Comparison to Free Radial Forearm Flap. J Oral Maxillofac Surg 75:2261-2269.

Werner JA, Schunke M, Lippert BM, Koeleman-Schmidt H, Gottschlich S, Tillmann B (1995) [The laryngeal lymph vessel system of the human. A morphologic and lymphography study with clinical viewpoints]. HNO 43:525-531.

White HN, Golden B, Sweeny L, Carroll WR, Magnuson JS, Rosenthal EL (2012) Assessment and incidence of salivary leak following laryngectomy. Laryngoscope 122:1796-1799.

Wiegand S, Wiemers C, Murthum T, Zimmermann AP, Bette M, Mandic R, Werner JA (2013) Risk of lymph node metastases after en bloc cold steel, en bloc laser-, and piecemeal laser surgical resection of auricular VX2 carcinoma. Lasers in medical science 28:1137-1141.

Wurdemann N, Wagner S, Sharma SJ, Prigge ES, Reuschenbach M, Gattenlohner S, Klussmann JP, Wittekindt C (2017) Prognostic Impact of AJCC/UICC 8th Edition New Staging Rules in Oropharyngeal Squamous Cell Carcinoma. Front Oncol 7:129.

Yao M, Nguyen T, Buatti JM, Dornfeld KJ, Tan H, Wacha J, Bayouth JE, Clamon GH, Funk GF, Smith RB, Chang K, Hoffman HT (2006) Changing failure patterns in oropharyngeal squamous cell carcinoma treated with intensity modulated radiotherapy and implications for future research. American journal of clinical oncology 29:606-612.

Yoshimura R, Kagami Y, Ito Y, Asai M, Mayahara H, Sumi M, Itami J (2010) Outcomes in patients with early-stage hypopharyngeal cancer treated with radiotherapy. International journal of radiation oncology, biology, physics 77:1017-1023.

Zhang B, Tu G, Xu G, Tang P, Hu Y (1999) Squamous cell carcinoma of temporal bone: reported on 33 patients. Head Neck 21:461-466.

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7 Anlage: Zugrundeliegende Originalarbeiten

1. **Weiss BG**, Ihler F, Pilavakis Y, Wolff HA, Canis M, Welz C, Steiner W (2017) Transoral laser microsurgery for T1b glottic cancer: review of 51 cases. Eur Arch Otorhinolaryngol 274:1997-2004.
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2. **Weiss BG**, Ihler F, Wolff HA, Schneider S, Canis M, Steiner W, Welz C (2017) Transoral laser microsurgery for treatment for hypopharyngeal cancer in 211 patients. Head Neck 39:1631-1638.
   Impact Factor: 2.471

3. **Weiss BG***, Ihler F*, Anczykowski MZ, Bertlich M, Kitz J, Steiner W, Canis M, Jakob M (2019) Transoral laser microsurgery for treatment of oropharyngeal cancer in 368 patients. Head Neck 41:3144-3158.
   Impact Factor: 2.442 (2018)

4. **Weiss BG**, Bertlich M, Canis M, Ihler F (2017) Transoral laser microsurgery or total laryngectomy for recurrent squamous cell carcinoma of the larynx: Retrospective analysis of 199 cases. Head Neck 39:1166-1176.
   Impact Factor: 2.471

5. Welz C, Canis M, Schwenk-Zieger S, Spiegel JL, **Weiss BG***, Pilavakis Y* (2017) Oral Cancer Reconstruction Using the Supraclavicular Artery Island Flap: Comparison to Free Radial Forearm Flap. J Oral Maxillofac Surg 75:2261-2269.
   Impact Factor: 1.779

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1

Weiss BG, Ihler F, Pilavakis Y, Wolff HA, Canis M, Welz C, Steiner W (2017) Transoral laser microsurgery for T1b glottic cancer: review of 51 cases. Eur Arch Otorhinolaryngol 274:1997-2004.
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HEAD AND NECK

Transoral laser microsurgery for T1b glottic cancer: review of 51 cases

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Abstract For the treatment of T1b glottic carcinoma, different treatment options, such as transoral laser microsurgery, open surgical techniques, and primary radiotherapy, are under discussion. In this context, the aim of the present study was to describe oncologic results and complication rates of transoral laser microsurgery in treatment of T1b glottic carcinoma. This is a retrospective unicenter chart review of patients treated at an academic tertiary referral center between 1986 and 2006. Fifty-one previously untreated T1b cases were exclusively treated by transoral laser microsurgery and included into this study, 47 were male, and 4 were female. The main outcome measures included local control rate and complications, overall, disease specific, and recurrence-free survival. The median follow-up period was 98 months. The 5-year local control rate was 90.2%; larynx preservation rate was 92.2%. No intra- or postoperative complications, such as wound infections, postoperative bleeding, hematoma, edema, and fistula development, were observed. A single patient required revision surgery due to synechia. Five-year survival rates were: overall 84.7%, disease specific 97.7%, and recurrence free 72.4%. Our data support the conclusion that transoral laser microsurgery is a considerable treatment option in T1b glottic carcinoma. The oncologic outcome was at least comparable to other treatment options, while the perioperative morbidity and complication rate were lower.

Keywords Transoral laser microsurgery (TLM) · Early glottic squamous cell carcinoma · Larynx · Carbon dioxide laser · Organ preservation

Abbreviations

SCC	Squamous cell carcinoma
TLM	Transoral laser microsurgery
RT	Radiotherapy

Introduction

Laryngeal cancer is of special interest for head and neck surgeons, radiotherapists, and oncologists. It is the most common head and neck malignancy (excluding skin cancer) and represents 20.9% of all head and neck cancers [1]. In glottic carcinomas, prognosis is superior compared to other tumor locations, since patients present early with symptoms, such as dysphonia. Moreover, metastasis is rare due to the rarity of lymphatic vessels [2]. Even though treatment is successful and disease-specific survival rates exceed 90%, there is no consensus regarding the standard of treatment. Patients are treated by diverse modalities, such as conventional open surgery, transoral laser microsurgery (TLM), or primary radiotherapy (RT) [3–5]. Most commonly early glottic cancer appears unilateral affecting one vocal cord. Bilateral category T1b disease rarely

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occurs, and the debate about the best treatment option is controversial.

The aim of this study was to assess the oncologic results and complication rates of transoral laser microsurgery for the treatment of bilateral early glottic cancer cases (T1b).

Patients and methods

Patients with previously untreated glottic squamous cell carcinoma (SCC) which were staged T1b [6] were treated exclusively by transoral laser microsurgery at an academic tertiary referral centre between 1986 and 2006. This study was performed by retrospectively reviewing our hospital's cancer database and existing medical records without any further inquiry or patient intervention. Data were extracted from the original medical records and analyzed anonymously. This study was approved according to national regulations on 29th February 2016 by the institutional review board of the University Medical Center Göttingen (*Ethik-Kommission der Universitätsmedizin Göttingen*), reference number 10/2/16An.

Patient demographics (age and sex), tumor growth (side, anterior commissure involvement, depth of invasion, and grade), treatment specifications, details on performed neck dissection, incidence and nature of complications, recurrence details (number of treatment failures, time to first recurrence, site, stage, and salvage therapy), and second primary tumors if present (location and treatment) were documented, retrospectively.

The final disease status was defined as: alive without disease, alive with disease, death not due to disease (intercurrent disease or second primary malignancy), or death due to T1b glottic SCC. The overall follow-up was defined as the time interval in months between primary surgery and the last consultation or the date of death.

Preoperative examinations and follow-up

Preoperative routine examination at first presentation consisted of a magnifying rigid or flexible endoscopic examination, phoniatric investigation with stroboscopy, as well as B-Scan neck ultrasonography to stage for nodal disease. TLM was preceded in all cases by panendoscopy under general anesthesia with the aim of excluding a second primary tumor in the aero- and upper digestive tract. Computed tomography of the neck and lungs to evaluate cartilage invasion and exclusion of second primary tumors was not routinely performed in the investigated time span. However, later, it became a standard preoperative examination.

Regular follow-up consisted of an ear, nose, and throat examination, including B-Scan neck ultrasonography. In the first 2-year follow-up, examinations were intended to take place every 3 months, unless patients developed new symptoms. After 2 years of being free of recurrence, the follow-up period was extended to every 6 months. After 5 years without a recurrence, the patient was considered being cured of disease. It is worth mentioning that follow-up continued for the majority of the patients after 5 years.

Operative technique

Modern carbon dioxide laser technique coupled to an operating microscope with an attached micromanipulator allows essentially bloodless dissection with minimal carbonization under high magnification. It, therefore, achieves a clear resection margin sparing as much healthy tissue as possible. The goal of this operative technique is to combine safe oncologic resection and best functional outcome. Details on transoral laser microsurgery of the larynx have been previously described [7, 8]. In summary, the initial tumor dissection allows evaluating the depth of invasion and resection is followed step by step dissecting all parts of the tumor. The tumor is then ideally dissected with a clear margin of 1–2 mm, but when invasion extends beyond 3 mm in depth, a safety margin of 2–3 mm is chosen. In the case of bilateral glottic carcinoma with healthy mucosa at the anterior commissure, resection in a single procedure was performed without risk of anterior commissure webbing. In the case of anterior commissure involvement, a two-step procedure was accomplished in a few selected cases, with the most prominent lesion excised first and the contralateral lesion excised 3–4 weeks later. This was performed to reduce the risk for webbing and the need for local aftercare, as described previously [7]. Anterior commissure involvement has the risk of underestimating the inferior and anterior tumor extension, which could result in a higher recurrence rate. Thus, adequate exposure was essential and a vertical incision at the anterior commissure was performed to evaluate whether the perichondrium or the soft tissue of the neck had been invaded and, if required, to remove parts of the cartilage and/or the cricothyroid membrane to ensure having a sufficient safety margin. A low laser power (2–4 W) was used for the delicate vocal cords, but was increased when resection of the cricothyroid membrane or thyroid cartilage at the anterior commissure was necessary (up to 14 W).

Antibiotics and corticosteroids were not given routinely. A bilateral selective neck dissection was performed in case of clinical suspicious neck disease (2 of 51 cases). No primary RT was used in the initial management of these patients.

Statistical methods

Follow-up data were available for all patients. In terms of the present study, alive patients were followed up

until January 2014, or until their date of death. The median follow-up period was 98 months (range 1–240 months). For calculating survival times, the interval between the date of surgery and an event was determined. Event in overall survival was the patients' death from all possible causes, whereas all patients alive were counted as censored observations. For disease-specific survival, only death from laryngeal cancer was an event. In recurrence-free survival, events were local and regional recurrences, distant metastasis, or death due to primary disease, whereas intercurrent death, death due to second primary tumors, or patients alive without recurrences was censored observations. For the local control rate, events were local or locoregional recurrences and being alive without local recurrences or death regardless of reason defined censored observations. We defined local recurrence either as carcinoma in situ or SCC occurring at least 3 months after the completion of primary treatment. Locoregional recurrence was defined as treatment failure occurring simultaneously within both the larynx and the cervical lymph nodes. Finally, isolated cervical lymph node recurrence was defined as regional failure. The endpoints for statistical analysis were recurrence free, overall, and disease-specific survival, the local control rate, and the rate of larynx preservation (absolute rate). For calculating survival rates, the method of Kaplan–Meier with a 95% confidence interval was used [9]. All statistics were analyzed using the STATISTICA Software, version 12.5 (StatSoft, Tulsa, OK, USA).

Results

Patients and therapy

In total, 51 patients with T1b glottic carcinoma treated between 1986 and 2006 matched the inclusion criteria, 47 were men (92%), and 4 were women (8%). The age ranged from 46 to 86 years with a median age of 63 years. Patient demographics are given in Table 1. All patients were exclusively treated by TLM. A selective bilateral neck dissection was performed in two cases (patient one level II, III; patient two levels II–IV), where preoperative ultrasonography was suspicious of neck disease. Histological both cases proved to be free of nodal involvement. Thus, all cases were staged pT1b c/pN0 M0. A histological proven negative resection margin status was achieved in all cases. The median depth of invasion was 2 mm (range 0.5–5 mm). The tumor grade was well differentiated in 5 cases (9.8%), moderately well differentiated in 42 cases (82.4%), and unknown in 4 cases (7.8%).

Table 1 Patient characteristics

Variables	No. of patients	%
Sex		
Male	47	92.2
Female	4	7.8
Age, years		
Median	63	
Range	46–86	
Localization		
Right side	4	7.8
Left side	3	5.9
Both sides	43	84.3
Median	1	2.0
Anterior commissure involvement	34	66.7
Depth of invasion, mm		
Median	2	
Range	0.5–5	
Unknown	17	33.3
Grade		
Well differentiated	5	9.8
Moderately well differentiated	42	82.4
Unknown	4	7.8
First recurrence, $n = 12$		
Local	11	21.6
Locoregional	1	2.0
Regional	–	
Second recurrence, $n = 5$		
Local	3	5.9
Locoregional	–	
Regional	2	3.9
Third recurrence, $n = 2$		
Local	1	2.0
Locoregional	–	
Regional	1	2.0
Second primary tumor, $n = 15$		
Head and neck region	2	3.9
Other region/organs	13	25.5

During the above-mentioned period, 11 patients (out of 62 T1b cases in total) with the diagnosis of T1b glottic cancer were not included into the study because of the following reasons: 2 suffered from a second primary tumor, 1 was previously treated for malignant disease (colorectal disease), 5 had recurrent or residual disease after primary treatment elsewhere, 1 had non-squamous cell carcinoma histology, and 2 were previously treated in another centre. All these excluded patients were treated by laser microsurgery as well. No patient received primary RT for T1b glottic carcinoma in our centre. Only one of the five

excluded patients with recurrent disease treated in another institution initially received primary RT in another centre.

Local and locoregional control

Disease recurrence occurred in 12 patients (23.5%), and 11 patients had local, one locoregional recurrence. The median time to first recurrence was 30.2 months (range 1.8–55.3 months). The tumor category for first recurrence was rT1 in seven patients (58.3%), rT2 in three patients (16.6%), and rT4 in two patients (16.6%). Salvage therapy occurring after the first failure (Table 2) consisted of laser microsurgical resection in nine cases, laser microsurgery and neck dissection in one case, total laryngectomy in one case, and total laryngectomy in combination with postoperative radiotherapy in one case. For patients with only one recurrence, status at the final follow-up was four patients alive and disease free, three patients dead from disease, and five patients dead of either intercurrent disease ($n = 3$) or a second primary disease ($n = 2$).

Despite treatment, a second recurrence occurred in five patients (9.8%), of whom three had a local and two a regional recurrence. None of these patients with a second recurrence received postoperative RT after surgical treatment of the first recurrence. The rT category for the second recurrence was rT1 in one and rT4 in two cases. Patients with regional disease had a pN3 and pN2c nodal status. Salvage therapy after the second failure for patients with local recurrence consisted of TLM in one patient, total laryngectomy, neck dissection and postoperative chemoradiotherapy in one patient as well as total laryngectomy and postoperative radiotherapy in one patient. For the two patients with regional recurrences, neck dissection and radiotherapy were performed. Disease status at the final follow-up of these five patients included one patient free of disease and alive, three patients dead due to disease, and one patient dead due to intercurrent disease (Table 2).

A third recurrence occurred in two patients (3.9%): one being local (rpT3pN0) and was treated by a total laryngectomy with neck dissection and the other regional (rpN3) which was treated by a neck dissection revision. The patient with the local recurrence was still alive and disease free at the last follow-up. The patient with the regional recurrence died from the disease. Figure 1 presents the local control rate (at 5 years 90.2%) after TLM for all patients.

Five patients required a total laryngectomy for salvage of recurrences after primary laser microsurgery (5 of 51 patients). The 5-year larynx preservation rate in patients with T1b glottic SCC treated with primary laser microsurgical resection was 92.2%.

Table 2 Salvage therapy after the first, second, and third treatment failures for all patients

Salvage therapy	No. of patients	%
Treatment modality first recurrence		
TLM	9	75.0
TLM + ND	1	8.3
LE + RT	1	8.3
LE	1	8.3
Total	12	100.0
Treatment modality second recurrence		
TLM	1	20
ND + RT	2	40
LE + ND	1	20
LE + RT	1	20
Total	5	100
Treatment modality third recurrence		
ND	1	50
LE + ND	1	50
Total	2	100

TLM transoral laser microsurgery, *ND* neck dissection, *RT* radiotherapy, *LE* total laryngectomy

Second primary tumors

After primary treatment of T1b glottic cancer, over time 15 patients were diagnosed with a second primary tumor (29.4%). Two were located in the head and neck regions (13.3%), six in the lung (40%), two in the urogenital tract (13.3%), one in the gastrointestinal tract (6.6%), and four patients developed skin tumors (26.6%).

Survival

The 5-year recurrence-free, overall, and disease-specific survival rates (Kaplan–Meier method) were 72.4, 84.7, and

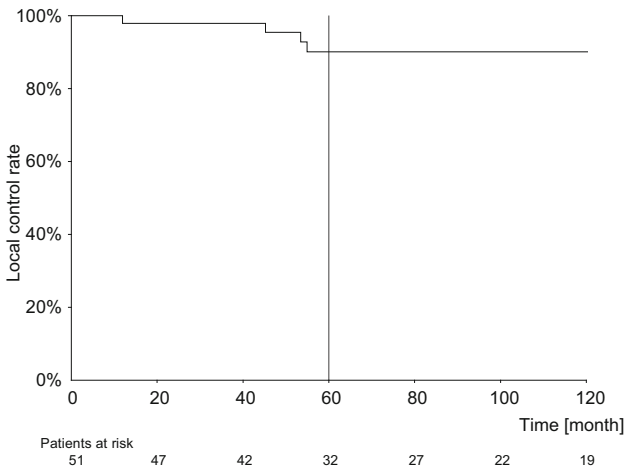

Fig. 1 Five-year Kaplan–Meier estimates for local control

97.7%, respectively (Fig. 2a–c). At the final follow-up for the entire group of patients with T1b glottic SCC, the overall disease status was 32 patients alive with no disease (62.7%), 3 patients died due to disease (5.9%), 16 patients died without disease (31.4%) of whom 9 died due to intercurrent death, and 7 due to a second primary tumor.

Postoperative management and complications

No intra- or postoperative complications, such as wound infections, postoperative bleeding, hematoma, edema, and fistula development, were observed.

In only one case, we observed profuse endolaryngeal scar tissue formation requiring a transoral revision surgery with mucosal tissue transplantation 3 months after the initial surgery. The same patient required a further revision, which was performed through a laryngofissure 1 year after the initial surgery because of synechia formation. No patient required a tracheostomy or a nasogastric feeding tube during the initial treatment.

Discussion

Transoral laser microsurgery was introduced by Strong and Jako [10] for the treatment of benign laryngeal lesions. In the following years, Steiner et al. developed the technique for malignant lesions of all categories and localizations [7, 8]. In 1993 Steiner [11] published his first long-term follow-up results of 240 patients with laryngeal carcinomas (pTis–pT4a) treated by TLM. Besides TLM, open chordectomy and partial laryngectomy are popular in some countries. Nevertheless, TLM has the advantage of a transoral approach with avoidance of trauma, time sparing technique, function preserving, low complication and morbidity rate, and short hospitalization. A third treatment

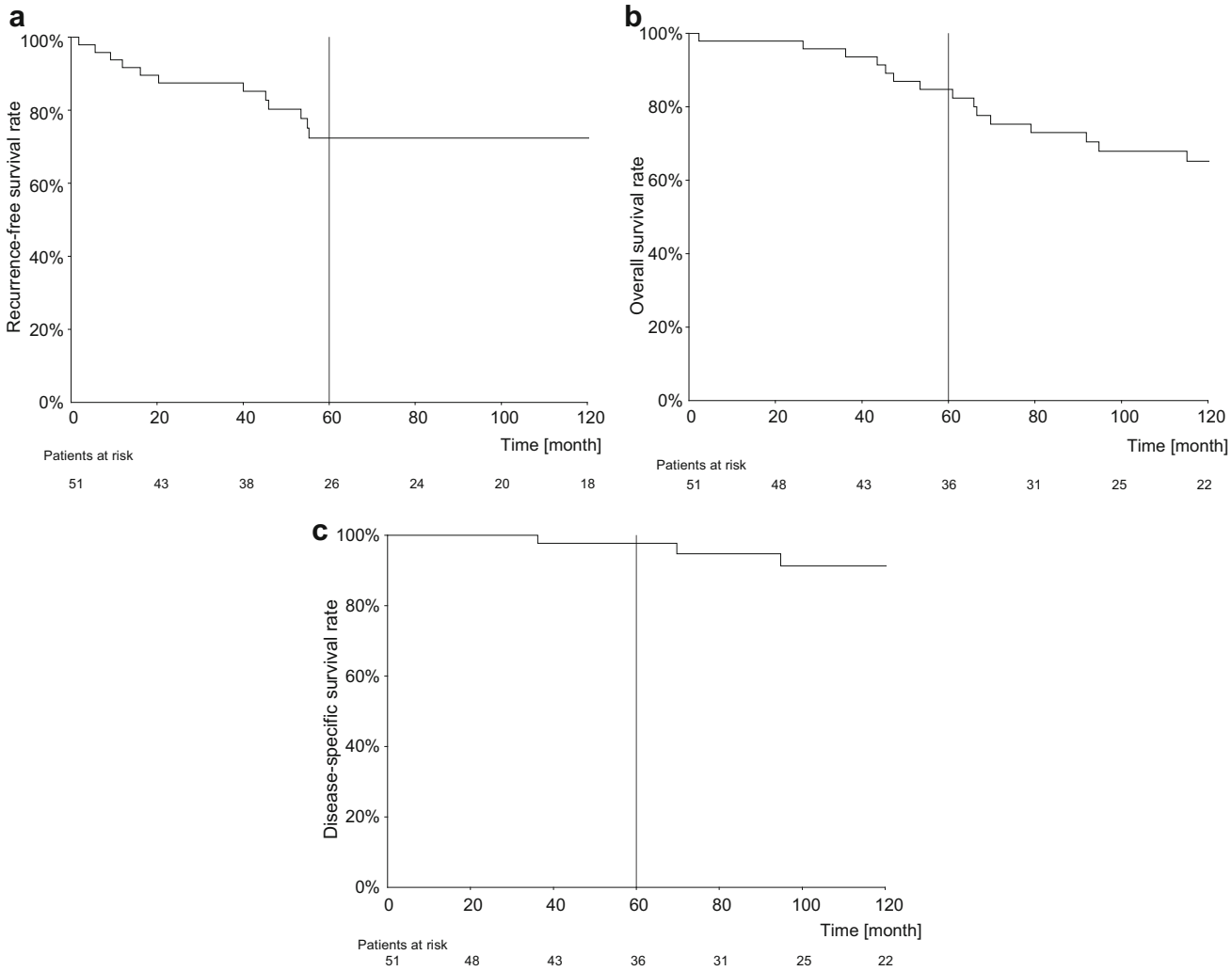

Fig. 2 **a** Five-year Kaplan–Meier estimates for recurrence-free survival. **b** Five-year Kaplan–Meier estimates for overall survival. **c** Five-year Kaplan–Meier estimates for disease-specific survival

strategy is primary RT. There is still considerable debate whether oncologic outcome after surgery is superior to primary radiotherapeutic strategies especially in locally circumscribed glottic cancer. No randomized controlled trial exists comparing TLM with other treatment strategies [12]. In retrospective analysis, comparison of treatment strategies is difficult due to diverse inclusion criteria and statistical outcome measures.

In our own series, when comparing the group of T1b patients with the more frequently occurring T1a cases treated by TLM, the following survival rates were observed: 5-year overall survival was 84.7% for T1b vs. 87.8% for T1a, disease-specific survival 97.7 vs. 98.0%, and recurrence-free survival 72.4 vs. 76.1%, respectively [13]. These results are in line with those of another centre that published their experiences with TLM for early laryngeal cancer affecting both vocal cords. In 39 T1b cases, the disease-specific survival at 5 years was 94.3% and the local control rate was 90.6%, which is nearly identical to our observation of 97.7 and 90.2%, respectively [3] (Table 3). We reviewed the international literature of the last two decades explicitly taking into account the studies presenting long-term (5-year) oncologic outcome with a cohort of more than 15 T1b cancer patients. There were often several limitations encountered in these studies. Small cohorts were presented and also patients with different tumor stages and categories were pooled together without presenting exclusive results for the T1b group. Therefore, under our criteria, for TLM, only a few publications were identified [3, 14, 15]. An overview of these studies is presented in Table 3. Oncologic outcome of our cohort was equal to other studies investigating TLM for early glottic cancer and was at least comparable to other treatment options.

The great advantage of the transoral approach for the treatment of laryngeal cancer is the low trauma to healthy tissue. In contrast, conventional open surgery requires dissection through the skin and disrupts the integrity of the cartilage to gain best exposure to the tumor site. Lei et al. [5] compared the middle frontal horizontal partial laryngectomy with the anterior frontolateral vertical partial laryngectomy for the treatment of T1b SCC. Oncologic results were comparable (see Table 3), whereas severe complications, such as laryngeal fistula (5.9%) and laryngeal stenosis (17.6%), followed the second procedure and subcutaneous emphysema, aspiration, and pneumonia occurred after both types of partial laryngectomies [5]. In comparative retrospective analysis, it was shown that complications were less frequent with TLM compared to open surgery [3]. This is comparable to our data, where the only complication occurred in a single patient that developed synechia. Even though in our cohort, a few patients received a two-step procedure to prevent anterior webbing, the risk of tumor growth in the meantime needs to be taken into consideration and does question this approach. A tracheostomy and a nasogastric feeding tube that are

Table 3 Studies of the last two decades presenting 5-year oncologic outcome with a cohort of at least 15 T1b cancer cases

References	Treatment strategy	No. of T1b cases	OS	DSS	RFS	LCR
Present study	TLM	51	84.7	97.7	72.4	90.2
Hoffmann et al. [15]	TLM	51	62.5	80.8	58.5	n/a
Marcotullio et al. [14]	TLM	39	87.2	n/a	n/a	n/a
Karatzanis et al. [3]	TLM	39	n/a	94.3	n/a	90.6
	frontolateral laryngectomy	22				
Lei et al. [5]	MFHPL	31	86.0	n/a	78.1	n/a
	AFVPL	34	85.1	n/a	81.9	n/a
Pignataro et al. [16]	horizontal glottectomy	37	85.4	n/a	91.0	n/a
Spector et al. [28]	mainly frontolateral hemilaryngectomy	50	n/a	n/a	n/a	87
Khan et al. [17]	RT	21	n/a	n/a	n/a	83
Hirasawa et al. [4]	RT or CRT	64	90.3	93.6	n/a	82.7
Chera et al. [18]	RT	72	83	99	n/a	93*
Jones et al. [19]	RT	20	78	100	n/a	95*
Harada et al. [20]	RT	26	96	n/a	n/a	83*
Nomiya et al. [21]	RT	48	89	93.4	n/a	85

Survival rates in percent

OS overall survival, *RFS* recurrence free survival, *DSS* disease-specific survival, *LCR* local control rate, *TLM* transoral laser microsurgery, *RT* radiotherapy, *CRT* chemoradiotherapy, *MFHPL* middle frontal horizontal partial laryngectomy, *AFVPL* anterior frontolateral vertical partial laryngectomy

* LCR after primary irradiation without salvage surgery (no asterisk when information is missing or vague)

obligatory in open surgical procedures [5, 16] are not required in TLM for the treatment of early glottic carcinoma. Thus, rapid recovery and short hospitalization time are an added advantage of TLM. In summery, due to the low complication rate and rapid recovery, age is not a contraindication for TLM, while it may be for external approaches.

As alternative to these surgical strategies, primary RT is often performed to treat early laryngeal cancer. One advantage is the avoidance of an operation, and thus, radiotherapy may be a treatment option for the elderly and/or multimorbid patients with high risk for general anesthesia. Nevertheless, in cases of residual disease, salvage surgery might also be employed. The local control rates at 5 years range from 82.7 to 95% [4, 17–21] (Table 3). However, it is not always obvious if the results concerning the oncologic outcome after primary RT also include patients treated additionally with salvage surgery for residual disease (Table 3, LCR with asterisk indicates results without salvage surgery). Moreover, the term salvage surgery is used for different scenarios, for example, completing the treatment after incomplete response (residual disease), but also for the treatment of local, regional, or locoregional recurrences [22]. In addition, authors use different stages, definition of end points, observation periods, statistics, and indication criteria for diverse treatment modalities. Thus, direct comparison of different treatment strategies is difficult.

We present our data regarding a homogeneous group of exclusively TLM-treated T1b glottic SCC patients. Prospective randomized trials are required, as comparative retrospective analysis of T1 glottic cancer cases treated by TLM or primary radiotherapy is often contradictory. The studies either present significant differences in the oncologic outcome and advise for surgery [23] or state an equivalent treatment outcome [24]. From the patient's point of view, it has to be considered that one successful transoral tumor resection is a short procedure under general anesthesia followed by a few days of hospitalized observation period and rapid recovery [25]. In contrast, radiotherapy involves a series of daily treatments usually for about 6 weeks. This not only is associated with greater actual costs, but also greater hidden costs in terms of total travel time and distance and the missed time at work [26]. Most publications state that no major complications occur during RT. The ones that list them specify only grade 1 and grade 2 radiation mucositis and radiation dermatitis to be frequent [4, 20].

Compared to primary RT, surgical strategies share the following advantages. The first important advantage of surgery is that a histological proven R0 resection can be achieved. Second, in case of recurrences, a further surgical treatment (including TLM) and also radiotherapeutic strategies (postoperative or primarily) are possible treatment options. In contrast, after the initial primary RT in case of residual disease or recurrences, the only remaining treatment option is surgery that could be even more radical, including a laryngectomy. The added advantage of primarily treating patients by TLM is that in case of recurrences, a second tumor resection meets non-irradiated tissue, and due to the previous low trauma of TLM, a nearly surgical untouched tissue. Moreover, a tracheotomy as performed during conventional surgery in many cases is not required for TLM. Both the previous irradiation and a tracheotomy were identified to be risk factors for severe complications, such as pharyngocutaneous fistulas [27]. These advantages need to be discussed with the patient even before primary treatment, since according to the present data and in the literature, recurrence occurred in 21.8–23.5% after TLM [14], 12.9–14.7% after more radical open procedures [5, 16, 28], and 8.3–18.8% after RT [18, 20, 21]. Even though the presented concept of treatment achieved a high rate of larynx preservation, especially after recurrent surgery the risk for dysphonia should, moreover, be taken into account in the decision of treatment strategy.

Given the fact that in our study, no patient needed a tracheostomy, nasogastric or gastrostomy tube after TLM, the airway and ability to swallow were unaffected. This arises from the ability of TLM to resect the tumor under microscopic magnification with the important characteristic of laser surgery to differentiate between healthy and affected tissue by the grade of carbonization at the cutting surface. Thus, TLM spares as much functionally important tissue as possible.

Conclusion

In our study, we present transoral laser microsurgery for T1b glottic cancer to have outcomes at least equivalent to conventional open surgery or primary RT. This, along with the advantages of minimal complications, minimal trauma to healthy tissue and the convenience of sparing a tracheostomy and nasogastric feeding tube could make it the technique of choice. Prospective randomized trials are needed to compare the oncologic outcomes in the above-mentioned treatment strategies, focusing also on the patients' quality of life and functional outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

References

1. Hoffman HT, Karnell LH, Funk GF, Robinson RA, Menck HR (1998) The National Cancer Data Base report on cancer of the head and neck. Arch Otolaryngol Head Neck Surg 124(9):951–962
2. Werner JA, Schunke M, Lippert BM, Koeleman-Schmidt H, Gottschlich S, Tillmann B (1995) The laryngeal lymph vessel system of the human. A morphologic and lymphography study with clinical viewpoints. HNO 43(9):525–531
3. Karatzanis AD, Psychogios G, Zenk J, Waldfahrer F, Hornung J, Velegrakis GA, Iro H (2009) Comparison among different available surgical approaches in T1 glottic cancer. Laryngoscope 119(9):1704–1708. doi:10.1002/lary.20537
4. Hirasawa N, Itoh Y, Naganawa S, Ishihara S, Suzuki K, Koyama K, Murao T, Asano A, Nomoto Y, Horikawa Y, Sasaoka M, Obata Y (2012) Multi-institutional analysis of early glottic cancer from 2000 to 2005. Radiat Oncol 7:122. doi:10.1186/1748-717X-7-122
5. Lei WB, Jiang AY, Chai LP, Zhu XL, Wang ZF, Wen YH, Su ZZ, Wen WP (2013) Middle frontal horizontal partial laryngectomy (MFHPL): a treatment for stage T1b squamous cell carcinoma of the glottic larynx involving anterior vocal commissure. PLoS One 8(1):e52723. doi:10.1371/journal.pone.0052723
6. Sobin LH, Compton CC (2010) TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer 116(22):5336–5339. doi:10.1002/cncr.25537
7. Steiner W, Haughey B, Bernal-Sprekelsen M (2013) Transoral laser microsurgery for cancer of the upper aerodigestive tract. Endo-Press, Tuttlingen
8. Steiner W, Ambrosch P (2000) Endoscopic laser surgery of the upper aerodigestive tract with special emphasis on cancer sugery. Thieme, Stuttgart
9. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 58:457–481
10. Strong MS, Jako GJ (1972) Laser surgery in the larynx. Early clinical experience with continuous CO_2 laser. Ann Otol Rhinol Laryngol 81(6):791–798
11. Steiner W (1993) Results of curative laser microsurgery of laryngeal carcinomas. Am J Otolaryngol 14(2):116–121
12. Warner L, Chudasama J, Kelly CG, Loughran S, McKenzie K, Wight R, Dey P (2014) Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. Cochrane Database Syst Rev 12:CD002027. doi:10.1002/14651858.CD002027.pub2
13. Canis M, Ihler F, Martin A, Matthias C, Steiner W (2014) Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. Head Neck. doi:10.1002/hed.23688
14. Marcotullio D, de Vincentiis M, Iannella G, Bigelli C, Magliulo G (2014) Surgical treatment of T1b glottic tumor, 10-years follow-up. Eur Rev Med Pharmacol Sci 18(8):1212–1217
15. Hoffmann C, Cornu N, Hans S, Sadoughi B, Badoual C, Brasnu D (2015) Early glottic cancer involving the anterior commissure treated by transoral laser cordectomy. Laryngoscope. doi:10.1002/lary.25757
16. Pignataro L, Capaccio P, Neglia CB, Ottaviani A (2000) Clinical experience with the treatment of T1b glottic cancer by means of horizontal glottectomy. Eur Arch Otorhinolaryngol 257(4):216–218
17. Khan MK, Koyfman SA, Hunter GK, Reddy CA, Saxton JP (2012) Definitive radiotherapy for early (T1–T2) glottic squamous cell carcinoma: a 20 year Cleveland Clinic experience. Radiat Oncol 7:193. doi:10.1186/1748-717X-7-193
18. Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM (2010) T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys 78(2):461–466. doi:10.1016/j.ijrobp.2009.08.066
19. Jones DA, Mendenhall CM, Kirwan J, Morris CG, Donnan A, Holwerda S, Kraus ST, Mann CJ, Grant JR, Donnan B, Mendenhall WM (2010) Radiation therapy for management of t1–t2 glottic cancer at a private practice. Am J Clin Oncol 33(6):587–590. doi:10.1097/COC.0b013e3181beaab0
20. Harada A, Sasaki R, Miyawaki D, Yoshida K, Nishimura H, Ejima Y, Kitajima K, Saito M, Otsuki N, Nibu K (2015) Treatment outcomes of the patients with early glottic cancer treated with initial radiotherapy and salvaged by conservative surgery. Jpn J Clin Oncol 45(3):248–255. doi:10.1093/jjco/hyu203
21. Nomiya T, Nemoto K, Wada H, Takai Y, Yamada S (2008) Long-term results of radiotherapy for T1a and T1bN0M0 glottic carcinoma. Laryngoscope 118(8):1417–1421. doi:10.1097/MLG.0b013e3181781791
22. Sanabria A, Kowalski LP, Shaha AR, Silver CE, Werner JA, Mandapathil M, Takes RP, Strojan P, Rinaldo A, Ferlito A (2014) Salvage surgery for head and neck cancer: a plea for better definitions. Eur Arch Otorhinolaryngol 271(6):1347–1350. doi:10.1007/s00405-014-2924-7
23. Markou K, Nikolaou A, Nalbadian M, Petridis D, Nicolaidis V, Daniilidis I (2002) How often is total laryngectomy necessary for the treatment of T1 failures after radiotherapy or cordectomy? Eur Arch Otorhinolaryngol 259(1):4–10
24. Dinapoli N, Parrilla C, Galli J, Autorino R, Micciche F, Bussu F, Balducci M, D'Alatri L, Marchese R, Rigante M, Di Lella G, Liberati L, Almadori G, Paludetti G, Valentini V (2010) Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population. Strahlenther Onkol 186(11):607–613. doi:10.1007/s00066-010-2142-1
25. Altuna X, Zulueta A, Algaba J (2005) CO_2 laser cordectomy as a day-case procedure. J Laryngol Otol 119(10):770–773. doi:10.1258/002221505774481200
26. Smith JC, Johnson JT, Cognetti DM, Landsittel DP, Gooding WE, Cano ER, Myers EN (2003) Quality of life, functional outcome, and costs of early glottic cancer. Laryngoscope 113(1):68–76. doi:10.1097/00005537-200301000-00013
27. Paydarfar JA, Birkmeyer NJ (2006) Complications in head and neck surgery: a meta-analysis of postlaryngectomy pharyngocutaneous fistula. Arch Otolaryngol Head Neck Surg 132(1):67–72. doi:10.1001/archotol.132.1.67
28. Spector JG, Sessions DG, Chao KS, Haughey BH, Hanson JM, Simpson JR, Perez CA (1999) Stage I (T1 N0 M0) squamous cell carcinoma of the laryngeal glottis: therapeutic results and voice preservation. Head Neck 21(8):707–717

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ORIGINAL ARTICLE

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Transoral laser microsurgery for treatment for hypopharyngeal cancer in 211 patients

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Abstract

Background: The oncologic and functional outcome of transoral laser microsurgery (TLM) for primary treatment of hypopharyngeal cancer was examined in a multimodal treatment concept.

Methods: Two hundred eleven patients with squamous cell carcinoma (SCC) of the hypopharynx (pT1-4a, pN0-2, M0) were treated by TLM +/− neck dissection (88%) +/− (chemo)radiotherapy ([C]RT; 51%). The majority of cases were advanced stages III and IVa (85%).

Results: The 5-year Kaplan-Meier estimates for local control after TLM were pT category-related 88.1%, 74.8%, 77.3%, and 61.8% for pT1-4a tumors. The 5-year estimates of overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) for early stages I and II were 68.2%, 96.7%, and 74.6%, respectively; for stage III they were 65.9%, 83.8%, and 56.4%, respectively; and the rates for stage IVa were 44.5%, 60.7%, and 50.3%, respectively. Overall, 95.7% of the patients maintained regular oral nutrition without feeding tube dependency.

Conclusion: Primary TLM in multimodal concepts of treatment (+/− neck dissection, +/− [C]RT) offers favorable oncologic results as compared with other therapeutic regimes.

KEYWORDS

carbon dioxide laser, hypopharynx, multimodal treatment concepts, pharyngeal squamous cell carcinoma, transoral laser microsurgery (TLM)

1 | INTRODUCTION

The proportion of hypopharyngeal cancer of head and neck malignancies is 4.3%.[1] The most common histological type is squamous cell carcinoma (SCC).[1] Treatment of pharyngeal cancer requires multimodal approaches consisting of surgery, chemo- and radiotherapy options. Primary treatment strategies include surgery or primary (chemo)radiotherapy ([C]RT). Regarding surgical treatment of hypopharyngeal cancer, different approaches (transoral or conventional open surgery) exist. If indicated, surgical treatment is accompanied by a unilateral or bilateral neck dissection and/or postoperative (C)RT. Transoral CO_2-laser microsurgery (TLM), initially introduced by Strong and Jako[2] for the treatment of small laryngeal lesions, was expanded by Steiner and coworkers from small to large tumors and to all regions of the upper aerodigestive tract.[3–8]

The purposes of this retrospective study were to assess the oncologic and functional results of TLM +/− neck dissection +/− postoperative (C)RT for the treatment of hypopharyngeal cancer and to compare this treatment strategy with common other multimodal treatment concepts.

2 | PATIENTS AND METHODS

2.1 | Patients

We retrospectively analyzed the medical records of 211 patients who were treated for SCCs of the hypopharynx by TLM, within the Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Göttingen, between August 1986 and May 2015. This study was performed by reviewing our hospital's cancer database and

existing medical records without any further inquiry or patient intervention. Data were extracted from the original medical records and analyzed anonymously. The institutional review board (Ethikkommission der Universitätsmedizin Göttingen) approved this study according to national regulations on February 29, 2016 (file reference number 10/2/16An). Every patient treated within the University Medical Center Göttingen gives written informed consent for anonymized analysis of the medical data before treatment.

Patients with previously untreated SCC of the hypopharynx (T1-4a, N0-2, M0) who underwent TLM with curative intent met the inclusion criteria. Tumors were staged according to the current classification of the Union for International Cancer Control (UICC)[9] and the American Joint Committee on Cancer.[10] For functional or technical reasons, contraindications of TLM were extensive involvement of both arytenoids, circumferential esophageal spread, or invasion of the carotid sheath. Moreover, TLM may be contraindicated because of limitations in tumor exposure by endoscopes like any kind of extensive trismus or vertebral fixation. Excluded from this study were 390 patients with malignancies of the hypopharynx because they were non-SCC tumors (n = 17) or had a medical history of a primary tumor elsewhere (n = 96), simultaneously second primary (n = 39), N3 neck disease (n = 64), simultaneous distant metastases (n = 18), recurrent disease of tumors treated elsewhere primarily (n = 24) or underwent primary laryngectomy (n = 17), primary open or combined surgical procedures with/without reconstruction (n = 8), primary (C)RT (n = 74), and palliative treatment (n = 33). Age was not an exclusion criterion for surgery with curative intent.

2.2 | Staging procedures

Preoperative examination consisted of rigid or flexible pharyngoscopy and magnifying laryngoscopy without sedation. For tumor extent and lymph node evaluation, patients underwent CT and ultrasonography of the neck. To complete staging, ultrasonography of the abdomen and chest X-ray or later chest CT-scan examination was performed to rule out other manifestations.

2.3 | Treatment of primary tumors

Before planned surgery, a panendoscopy was performed with the patients under general anesthesia to assess the extent of the primary tumor and exclude any second primary tumors of the upper aerodigestive tract. Tissue was harvested for histology as well. TLM was performed with the CO_2-laser in continuous superpulse mode. Resections were done using the technique described by Steiner et al.[3,11,12] In brief, the principle of TLM involves a step-by-step resection with cutting through the tumor, allowing the surgeon to accurately inspect the boundary between normal and abnormal tissue under microscopic magnification. Thus, the surgeon is able to preserve as much healthy tissue as possible and to inspect the depth of invasion intraoperatively. Best visualization is achieved using different closed and distending laryngo-pharyngoscopes. Moreover, the differentiation between tumor and healthy tissue is feasible by evaluating the cutting characteristics (eg. carbonization) under microscopic magnification. Thereby an appropriate resection margin could be maintained of at least 5 mm, if possible 10 mm. In certain cases of very large tumors, it was not possible to adhere to 5-10 mm margins. In all the cases, sampling from the tumor bed for frozen section analyses ensured an R0 resection status. If final histology revealed margins <3 mm, the indication for a re-resection was discussed with the patient because of the high risk of submucosal tumor growth and low risk of functional impairment.

2.4 | Histological assessment

For histological assessment, specimens of the primary tumors were routinely examined in vertical 3-4 mm serial sections for evaluation of R0 resection. Neck dissection specimens were routinely investigated for nodal involvement.

2.5 | Diagnosis and treatment of the neck

Patients were assessed for potential lymph node metastasis, as described above. In patients with small tumors (pT1) and clinically unsuspicious lymph nodes, a watch-and-wait regime was performed and follow-up consisted of periodic ear, nose, and throat (ENT) examination, including neck ultrasonography. If the patient presented with advanced primary disease and the tumor infiltration depth was >3 mm, or if preoperative imaging revealed suspicious lymph nodes, a mainly selective neck dissection was performed. Bilateral neck dissections were carried out if (1) imaging revealed suspicious lymph nodes bilaterally, or (2) the primary tumor had an advanced stage with midline localization, or (3) if suspicious lymph nodes were seen only on one side but no postoperative (C)RT was planned because of a small primary tumor.

2.6 | Postoperative (chemo)radiotherapy

Postoperative (C)RT was mainly performed in cases of advanced neck disease (pN2a/b/c) or when the histopathological examination revealed extracapsular spread and/or lymphangiosis carcinomatosa. Because of the long period of retrospectively analyzed patients, according to further development of radiooncology in the time span from 1986 to 2015, patients were treated using different techniques and schemes, as described previously.[5]

2.7 | Follow-up

Regular follow-up consisted of ENT examination, including neck ultrasonography. The initially performed imaging (CT or MRI) was repeated yearly, or if there were clinical concerns, during the first 2 years of follow-up to detect cases of submucosal tumor recurrence. After 5 years without recurrences, a patient was considered as being healed.

2.8 | Statistical methods

Depending on the outcome value, for descriptive analysis, the mean value with corresponding SD, median, or frequencies (percentages) were chosen. Postoperative follow-up data were available for all

TABLE 1 Distribution of postoperative T and N categorization

	No. of patients (%)					
	c/pN0	pN1	pN2a	pN2b	pN2c	Total
pT1	11 (5)	9 (4)	2 (1)	6 (3)	0 (0)	28 (13)
pT2	22 (10)	11 (5)	0 (0)	15 (7)	5 (2)	53 (25)
pT3	31 (15)	13 (6)	2 (1)	43 (20)	6 (3)	95 (45)
pT4a	3 (1)	13 (6)	1 (1)	16 (8)	2 (1)	35 (17)
Total	67 (32)	46 (22)	5 (2)	80 (38)	13 (6)	211 (100)

patients. Recurrence was defined as disease occurring >3 months after the completion of initial curative surgery, whereas <3 months was counted as residual tumor. Late metastasis was defined as a lymph node disease occurring after initially clinical or histological negative neck (cN0/pN0), whereas recurrent metastasis occurred after the initial surgical treatment and a histological confirmed neck disease (pN+). For comparing survival rates across the different groups, the method of Kaplan-Meier with a 95% confidence interval was used.[13] The end points assessed were overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and the rate of local control. For calculating OS, the interval between the date of surgery and the date of death from all possible cases was defined, whereas the interval between the date of surgery and the last follow-up was counted as censored. For DSS, only death from pharyngeal cancer was seen as an event. In RFS, events were defined as local and regional recurrences, distant metastasis, and death because of primary disease, whereas intercurrent death, death because of second primary tumors, and patients alive without recurrences were counted as censored observations. For the local control rate, events were local recurrences. Being alive without local recurrences or death regardless of reason defined censored observations. Statistical differences between groups were calculated by the log-rank test. A value of $P < .05$ was considered to be statistically significant. All analyses were performed using the software Dell Statistica version 12 (Dell, Round Rock, TX).

3 | RESULTS

3.1 | Patients and therapy

Two hundred eleven patients diagnosed with hypopharyngeal cancer met the inclusion criteria (22 women and 189 men; ratio 1:8.6). If tumors spread between the oropharynx and the hypopharynx or infiltrated the larynx, then the primary site was defined by the surgeon according to the main localization. Distribution and frequency of the sublocations for hypopharyngeal tumors were 75.4% piriform sinus (n = 159), 10.9% aryepiglottic fold (n = 23), 5.2% postcricoid area (n = 11), and 8.5% posterior wall (n = 18). Mean age at diagnosis was 57.4 ± 9.4 years (range 33-92 years). Stage distribution was 5.2% (n = 11), 10% (n = 21), 30.8% (n = 65), 54% (n = 114) for UICC stages I-IVa, respectively. Postoperative T category distribution was 13.3% (n = 28) for pT1, 25.1% (n = 53) for pT2, 45% (n = 95) for pT3, and 16.6% (n = 35) for pT4a. Distribution of postoperative T and N categorization is shown in Table 1.

Every patient was treated by TLM. Nineteen patients were exclusively treated by laser surgery (9%), 84 had TLM and a unilateral or bilateral neck dissection (39.8%), 6 only received TLM and postoperative (C)RT (2.8%), whereas 48.3% received TLM, a neck dissection, and (C)RT (102 patients). A neck dissection was performed in 186 patients (88%), 66.7% (n = 124) unilateral and 33.3% (n = 62) bilateral to the primary tumor site. In the mostly selective neck dissections, levels II and III were included in all but 2 cases. Additionally, level I (n = 8) and/or level IV (n = 99) and/or level V (n = 25) was completed in 105 (42.3%) of 248 neck sides. Modified radical neck dissection was performed in 4 patients (1.6%) and radical neck dissection in 8 patients (3.2%). Histological assessment revealed positive lymphatic nodes in 144 patients (77.4%) with 13 cases of bilateral disease (7%). Extracapsular spread of tumor occurred in 42 cases. Postoperative radiotherapy was given to 108 patients (51%), in 40 cases combined with chemotherapy (19%), because knowledge leading to more standardized recommendations for concomitant CRT was only developing in the long time span of this retrospective analysis from 1986 to 2015.

Mean follow-up time until death or the patient was lost to follow-up was 64.6 ± 49 months with a maximum of 281 months.

3.2 | Oncologic results

At the time of the last follow-up of all 211 patients, 38.4% (n = 81) were still alive and free of disease, 2.4% (n = 5) were living with tumors, 16.6% (n = 35) had died intercurrently, 25.1% (n = 53) had died from disease, and 17.5% (n = 37) had died because of a second primary tumor. Treatment failures appeared in 35% (n = 73). The sites and numbers of first treatment failures are listed in Table 2. As shown, in 45 cases (21%), local or locoregional recurrence occurred. The 5-year local control rate after TLM was 88.1% for pT1, 74.8% for pT2, 77.3% for pT3, and 61.8% for pT4a tumors, as shown in Figure 1.

Second primary tumors developed in 60 of all 211 patients (28%). In 35%, these tumors were located in the ENT area (n = 21). Other primary sites were the lungs (28%; n = 17), esophagus (12%; n = 7), gastrointestinal tract (5%; n = 3), urogenital system (5%; n = 3), and other (15%; n = 9).

For all 211 patients diagnosed with hypopharyngeal cancer, Figure 2 depicts stage-related OS, DSS, and RFS. Table 3 shows the

TABLE 2 Sites and numbers of first treatment failures

Site	No. of patients	Percentage
Local recurrence	33	16
Local and regional recurrence	12	6
Late metastasis	8	4
Contralateral late metastasis	5	2
Recurrent metastasis	15	7
Total	73	35

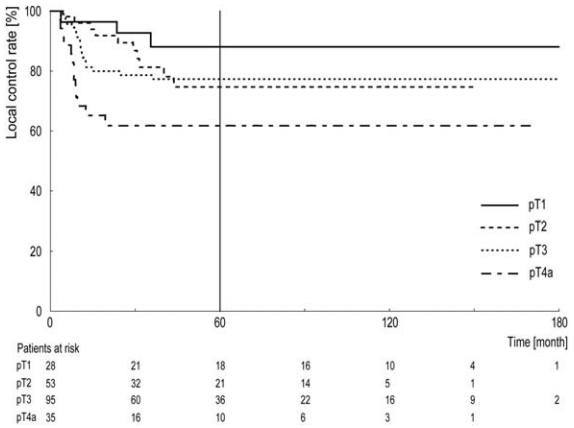

FIGURE 1 Five-year Kaplan-Meier estimates for local control related to pT-category. Patients at risk are shown below the diagrams

oncologic results for patients with hypopharyngeal cancer, in total, stage, and pT category related.

To analyze the influence of postoperative (C)RT, there were 75 patients with advanced disease (pT3-4 and/or pN+) who did not get postoperative (C)RT compared with 104 patients with advanced disease who got the postoperative treatment. In this group of 179 patients, those who actually received postoperative (C)RT showed a significantly better outcome in the estimates for RFS and local control (Table 4 and Figure 3).

3.3 | Postoperative management and complications

To diminish the risk for aspiration pneumonia, a nasogastric feeding tube is placed when temporarily severe functional problems can be expected because of the locally advanced tumor spread. Therefore, a nasogastric feeding tube was placed postoperatively in 158 patients (75%) to maintain oral nutrition in the phase of wound healing. The median duration was 11 days with a range of 1-110 days. Twenty-one (10%) gastrostomy tubes had to be placed because of severe dysphagia and recurrent aspiration after surgery or (C)RT without sufficient subsequent improvement. In 12 patients (5.7%), the gastrostomy tube was necessary just temporarily and could be removed after a median duration of 18 months (range <1-147 months). The remaining 9 patients (4.3%) had the permanent tube until their death or the day of the last follow-up. Nasogastric feeding tubes and gastrostomy tubes were only removed when the patients were able to eat sufficiently and had no clinical and/or radiologic signs of aspiration.

Postoperative bleeding after TLM occurred in 22 patients (10.4%) and could be managed in most cases by transoral electrocoagulation or clipping. In 1 case, ligation of a branch of the external carotid artery was necessary.

A tracheotomy was necessary in 8 cases (3.8%), mostly when postherapeutic (surgery or [C]RT) edema and consecutive dyspnea occurred. Pharyngeal fistulas occurred in 2 patients (0.9%) with 1 surgical intervention being necessary (local muscle flap) during the initial tumor resection with simultaneous neck dissection. In the second case,

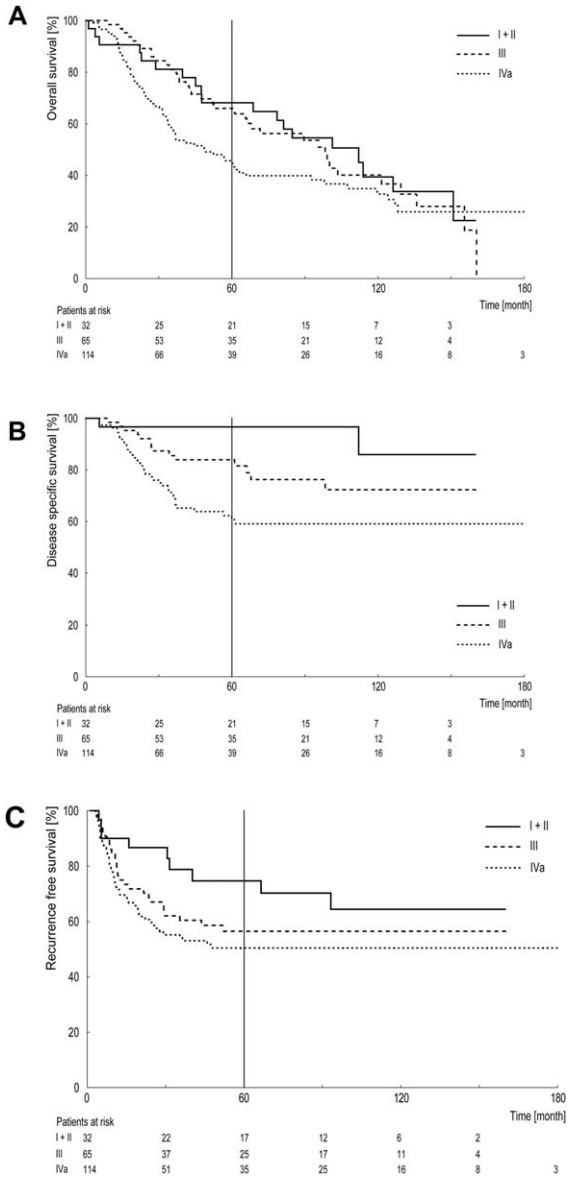

FIGURE 2 Five-year Kaplan-Meier estimates for A, overall survival, B, disease-specific survival, and C, recurrence-free survival stages related for 211 patients with hypopharyngeal cancer. Patients at risk are shown below the diagrams

TABLE 3 Five-year oncologic results (in percentages) for patients with hypopharyngeal cancer stage and pT category related

	% by pT category and tumor classification (UICC)								
	pT1	I-II	pT2	III	pT3	IVa	pT4a	I-IVa	pT1-pT4a
OS	77.6	68.2	52.8	65.9	56.7	44.5	34.0	55.0	55.0
RFS	77.9	74.6	49.8	56.4	57.8	50.3	40.1	55.9	55.9
DSS	96.3	96.7	75.4	83.8	76.5	60.7	45.9	74.1	74.1
Local control rate	88.1		74.8		77.3		61.8		75.7

Abbreviations: DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival.

TABLE 4 Distribution of 179 patients with indication or recommendation for postoperative (chemo)radiotherapy (pN+; pT3-4)

	III + IVa	pT3 + pT4a
(C)RT yes	104	76
(C)RT no	75	54
P value local control rate	**.027**	**.04**
P value RFS	**.035**	.081

The group receiving postoperative (C)RT showed a significantly better outcome in the estimates for 5-year local control rates and RFS. Abbreviations: (C)RT, (chemo)radiotherapy; RFS, recurrence-free survival. The *P* values for local control rates and RFS comparing the group actually receiving (C)RT and the group that did not (significant *P* values in boldface letters).

conservative management was sufficient. For functional reasons, a laryngectomy needed to be performed in 1 patient (0.5%).

4 | DISCUSSION

For primary management of hypopharyngeal cancer, surgical strategies like conventional open surgery or transoral approaches, including TLM and recently also robotic surgery, are performed. If indicated, surgical treatment is accompanied by neck dissection and (C)RT. An alternative treatment is primary CRT. The lack of prospective randomized trials makes comparison of these approaches difficult. Moreover, different stages, end points, observation periods, statistics, and indication criteria for diverse treatment modalities make it difficult to compare the effectiveness of one treatment over the other. The purpose of this study was to assess TLM for primary management of early and advanced carcinomas of the hypopharynx under particular consideration of multimodal treatment concepts.

In our cohort, patients were exclusively treated by TLM (+/− neck dissection +/− [C]RT), as it has become a standard treatment strategy for laryngeal and pharyngeal cancer in many centers. Even though TLM offers a surgical option because all regions of the hypopharynx are accessible,[3,12] the literature lacks studies with large patient cohorts and long follow-up, especially for advanced-stage cancers. In our large series of 211 cases with 85% advanced-stage tumors, 5-year DSS was 74.1%, comparable to 76% described by Kuo et al[14] and 58% by Rudert and Höft[15] (Table 5).[14–21]

Ablative regimes for hypopharyngeal cancer, such as total laryngopharyngectomies, followed by reconstruction and (C)RT are common. Five-year DSS of 52% was reported for a cohort with comparable tumor size and stage to ours (n = 180; 90% advanced-stage hypopharyngeal cancer) that was treated by open surgery with reconstruction performed by a free jejunal interposition graft.[16] Anyhow, TLM is suitable for subsequent reconstructions as well, offering laryngeal preservation. Options for the treatment of large pharyngeal defects include the radial forearm free flap, the pectoralis major myocutaneous flap, or the supraclavicular artery island flap.[22,23]

Open surgical approaches to treat pharyngeal cancer were evaluated in different studies of the last decade. Kuo et al[14] studied cases with open partial laryngopharyngectomies for hypopharyngeal cancer. Oncologic outcome of open surgery is comparable to TLM (Table 5).[14–21] Direct comparison of 2 cohorts with hypopharyngeal cancer being treated by TLM or open partial laryngopharyngectomy (+/− neck dissection +/− [C]RT) in a single institution study was performed by Kuo et al.[14] Oncologic outcome was comparable with a 5-year OS of 48% versus 67% and a DSS of 65% versus 76% for open or laser surgery, respectively. However, in comparison, TLM resulted in better functional outcome with significant shorter time requiring a tracheal tube, time returning to oral alimentation, reduced hospitalization, and a higher laryngeal preservation rate (92% vs 71%).[14]

A low complication rate is one advantage of TLM. In our study, the most common complications were postoperative bleeding that occurred in 10.4% and could be managed in the majority of cases by transoral electrocautery or clipping. This is in line with the results of another study investigating TLM for hypopharyngeal cancer.[24] Moreover, large tumors (T3-T4) and localization in the hypopharynx have a significant higher risk for complications after TLM.[25] Only 2 cases (0.9%) of pharyngeal fistula formation were observed and just 1 case that needed surgical intervention, which is a very low rate compared to 7.1% and 10% occurring after open surgery.[14,16]

A relatively new minimal invasive treatment option is transoral robotic surgery that promises advantages because of a 3D view on the operation site and low morbidity of the transoral approach. One study

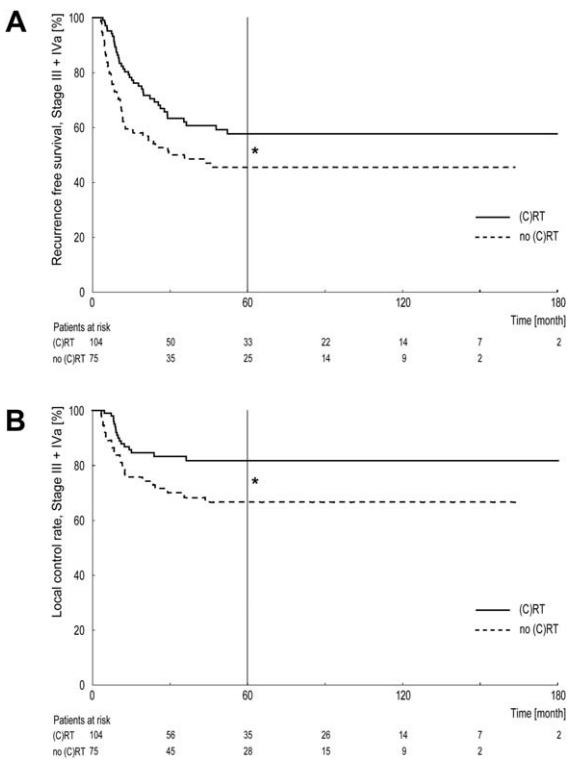

FIGURE 3 Five-year Kaplan-Meier estimates for A, recurrence-free survival of stages III-IVa, and B, local control of stages III-IVa of the patients with the indication or recommendation for postoperative (chemo)radiotherapy ([C]RT) that received or did not receive this adjuvant treatment modality. *P value $< .05$. Patients at risk are shown below the diagrams

TABLE 5 Overview of studies evaluating different treatment strategies of patients with tumors of the hypopharynx

Study	Treatment	No. of patients	Follow-up	Comment	Stage (UICC)	TNM	OS, %	RFS, %	DSS, %	Local control rate, %
Present study	1	211	5-y		I-IV (85% III-IV)	pT1-4	I-II = 68, III = 66, IVa = 45, I-IVa = 55	I-II = 75, III = 56, IVa = 50, I-IVa = 56	I-II = 97, III = 84, IVa = 61, I-IVa = 74	pT1 = 88, pT2 = 75, pT3 = 77, pT4a = 62, pT1-4a = 76
Kuo et al[14] 2013	1	25	5-y		I-IV	pT1-3 (36% T3)	67		76	
	2	28		Partial laryngopharyngectomy	I-IV	pT1-3 (21% T3)	48		65	
Rudert and Höft[15] 2003	1	29	5-y		I-IV	pT1-4 (7% pT3-4)	48	82	58	72
Bova et al[16] 2005	2	180	5-y	Total laryngopharyngectomy	90% III-IV	pT1-4	33	53	52	18
Park et al[17] 2012	3	23	3-y			pT1-4	89	84		
Godballe et al[18] 2002	4	101	5-y		91% III-IV	T1-4	18	17	31	
Yoshimura et al[19] 2010	5	77	5-y	16 patients with second primary tumors included	I-II	T1-2	47	57	74	70
Nakamura et al[20] 2006	5	95	5-y	Patients without synchronous tumors	I-II	T1-2	66		77	
Rabbani et al[21] 2008	6	123	5-y		I-IV	T1-2	I-II = 58, III = 43, IVa = 31, IVb = 13		I-II = 85, III = 73, IVa = 62, IVb = 22	T1 = 87 T2 = 83

Abbreviations: DSS, disease-specific survival; OS, overall survival; RFS, recurrence-free survival; UICC, Union for International Cancer Control.
Follow-up in years; OS, RFS, DSS, and local control rates in percentages.
Treatment approaches: 1 = transoral laser microsurgery (TLM) +/− neck dissection +/− (chemo)radiotherapy ([C]RT); 2 = open surgery +/− neck dissection +/− (C)RT; 3 = transoral robotic surgery +/− neck dissection +/− CRT; 4 = primary radiotherapy +/− salvage surgery; 5 = primary (chemo)radiotherapy; 6 = primary radiotherapy +/− neck dissection.

presented a cohort of 23 patients with mainly early hypopharyngeal carcinomas (70% T1 and T2 cases) treated by transoral robotic surgery +/− neck dissection +/− (C)RT. A negative margin was not achieved in 2 of the T4 cases with recurrent disease and previously received radiotherapy. Three-year OS and RFS was 89% and 84%, respectively[17] (Table 5).[14–21] For comparison of oncologic and functional outcome, further studies with larger patient cohorts, 5-year follow-up data, as well as survival rate calculations separated into T categories and stages are required.

Hypopharyngeal cancer often is divided into resectable and nonresectable cases, the latter might be treated primarily by (C)RT (primary CRT) +/− salvage surgery. Nevertheless, primary CRT might also be a treatment option for cancer that would be surgically resectable. Modern techniques and protocols follow the goal of best tumor control, such as maximal sparing of healthy tissue to diminish toxicity. Nevertheless, for advanced-stage disease, oncologic outcome is still poor (5-year OS of 18%, RFS of 17%, and DSS of 31%), thus being concluded by Godballe et al[18] that other treatment modalities have to be considered. In early-stage disease, primary CRT achieves good oncologic outcome and is an alternative treatment strategy,[19–21] however, sharing the toxicity of this high-dose irradiation, the results do not exceed those of surgical approaches, as shown in the present study. An overview about the oncologic results of primary CRT is given in Table 5.[14–21]

In oncologic centers, nowadays, multimodal treatment concepts are decided in an interdisciplinary consensus comprising surgical approaches and postoperative (C)RT to achieve the best oncologic outcome for our patients. Today postoperative (C)RT is the standard treatment approach in cases of advanced tumor size pT3-4 and/or at least pN2 neck disease.[26,27] Nevertheless, there is still debate whether small tumors with a single lymph node metastasis (pT1-2 pN1) should receive postoperative radiotherapy, thus a prospective randomized multicenter clinical trial is currently ongoing (ClinicalTrials.gov Identifier: NCT00964977). In the present study, postoperative (C)RT was mainly performed in cases of advanced neck disease (N2a/b/c) or when the histopathological examination revealed extracapsular tumor spread and/or lymphangiosis carcinomatosa. Due to the existence of a large cohort of advanced diseased patients that did not receive postoperative (C)RT (based on the current state of knowledge they might today receive (C)RT) the current data provide the unique opportunity to directly evaluate the impact of postoperative (C)RT on long-term survival within a patient cohort that will most likely not be available again. In this group of 179 patients, those who actually received (C)RT had a significant better outcome in RFS and local control rate. These results underline the today's guidelines for postoperative (C)RT being a valid additional treatment for advanced-stage disease.

Despite the 85% of advanced cases in the present study, the multimodal treatment concepts that comprised TLM, neck dissection, and, in many cases, postoperative (C)RT resulted in a good functional outcome, including the ability of oral alimentation with only 4.3% requiring a permanent gastrostomy tube. Even though a gastrostomy tube had to be placed temporarily in 10% of the patients, in comparison, for primary (C)RT it is routinely placed in all patients and more often lasts forever.[28] Moreover, compared to open surgery, patients treated by TLM require a significantly shorter time for returning to oral alimentation.[14]

Last, with just 1 patient who needed a laryngectomy for functional reasons, the laryngeal/organ preservation rate was very high in the present study.

Limitations of this study are the retrospective design. Additionally, no direct comparison to alternative strategies was possible because equally large patient cohorts were not available at our center. The strength is the largest cohort of hypopharyngeal cancer cases in literature so far. The direct comparison of advanced disease cases sharing the recommendation for postoperative (C)RT that did or did not receive this additional treatment underlines today's guidelines.

In conclusion, we demonstrated primarily TLM in multimodal concepts of treatment +/− neck dissection, +/− (C)RT to offer good oncologic results for the treatment of even advanced-stage hypopharyngeal cancer. Even though the oncologic outcome of different treatment strategies is hard to compare because studies with equally large patient cohorts are rare and they often address heterogeneous groups, different stages, and end points, the oncologic outcome of TLM exceeds a primary radiotherapeutic approach. Treatment strategies should be determined in interdisciplinary conferences and compared in prospective randomized trials with the patients' quality of life to be considered in future investigations.

REFERENCES

[1] Hoffman HT, Karnell LH, Funk GF, Robinson RA, Menck HR. The National Cancer Data Base report on cancer of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998;124(9):951–962.

[2] Strong MS, Jako GJ. Laser surgery in the larynx. Early clinical experience with continuous CO 2 laser. *Ann Otol Rhinol Laryngol*. 1972; 81(6):791–798.

[3] Steiner W. Experience in endoscopic laser surgery of malignant tumours of the upper aero-digestive tract. *Adv Otorhinolaryngol*. 1988;39:135–144.

[4] Steiner W, Ambrosch P, Hess CF, Kron M. Organ preservation by transoral laser microsurgery in piriform sinus carcinoma. *Otolaryngol Head Neck Surg*. 2001;124(1):58–67.

[5] Canis M, Ihler F, Wolff HA, Christiansen H, Matthias C, Steiner W. Oncologic and functional results after transoral laser microsurgery of tongue base carcinoma. *Eur Arch Otorhinolaryngol*. 2013;270(3): 1075–1083.

[6] Canis M, Martin A, Ihler F, et al. Transoral laser microsurgery in treatment of pT2 and pT3 glottic laryngeal squamous cell carcinoma - results of 391 patients. *Head Neck*. 2014;36(6):859–866.

[7] Canis M, Ihler F, Martin A, Matthias C, Steiner W. Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. *Head Neck*. 2015;37(6):889–895.

[8] Canis M, Ihler F, Martin A, Wolff HA, Matthias C, Steiner W. Organ preservation in T4a laryngeal cancer: is transoral laser microsurgery an option? *Eur Arch Otorhinolaryngol*. 2013;270(10):2719–2727.

[9] Sobin LH, Compton CC. TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. *Cancer*. 2010; 116(22):5336–5339.

[10] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–1474.

[11] Steiner W, Ambrosch P. *Endoscopic laser surgery of the upper aerodigestive tract: with special emphasis on cancer surgery*. Stuttgart, Germany and New York: Thieme; 2000.

[12] Steiner WH, Howard D, Haughey B, Bernal-Sprekelsen M, Gagstatter F. *Transoral Laser Microsurgery for Cancer of the Upper Aerodigestive Tract*. Tuttlingen, Germany: Endo-Press; 2013.

[13] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.

[14] Kuo CL, Lee TL, Chu PY. Conservation surgery for hypopharyngeal cancer: changing paradigm from open to endoscopic. *Acta Otolaryngol*. 2013;133(10):1096–1103.

[15] Rudert HH, Höft S. Transoral carbon-dioxide laser resection of hypopharyngeal carcinoma. *Eur Arch Otorhinolaryngol*. 2003;260(4):198–206.

[16] Bova R, Goh R, Poulson M, Coman WB. Total pharyngolaryngectomy for squamous cell carcinoma of the hypopharynx: a review. *Laryngoscope*. 2005;115(5):864–869.

[17] Park YM, Kim WS, De Virgilio A, Lee SY, Seol JH, Kim SH. Transoral robotic surgery for hypopharyngeal squamous cell carcinoma: 3-year oncologic and functional analysis. *Oral Oncol*. 2012;48(6):560–566.

[18] Godballe C, Jørgensen K, Hansen O, Bastholt L. Hypopharyngeal cancer: results of treatment based on radiation therapy and salvage surgery. *Laryngoscope*. 2002;112(5):834–838.

[19] Yoshimura R, Kagami Y, Ito Y, et al. Outcomes in patients with early-stage hypopharyngeal cancer treated with radiotherapy. *Int J Radiat Oncol Biol Phys*. 2010;77(4):1017–1023.

[20] Nakamura K, Shioyama Y, Kawashima M, et al. Multi-institutional analysis of early squamous cell carcinoma of the hypopharynx treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;65(4):1045–1050.

[21] Rabbani A, Amdur RJ, Mancuso AA, et al. Definitive radiotherapy for T1-T2 squamous cell carcinoma of pyriform sinus. *Int J Radiat Oncol Biol Phys*. 2008;72(2):351–355.

[22] Alves HR, Ishida LC, Ishida LH, et al. A clinical experience of the supraclavicular flap used to reconstruct head and neck defects in late-stage cancer patients. *J Plast Reconstr Aesthet Surg*. 2012;65(10):1350–1356.

[23] Welkoborsky HJ, Deichmüller C, Bauer L, Hinni ML. Reconstruction of large pharyngeal defects with microvascular free flaps and myocutaneous pedicled flaps. *Curr Opin Otolaryngol Head Neck Surg*. 2013;21(4):318–327.

[24] Vilaseca I, Blanch JL, Bernal-Sprekelsen M, Moragas M. CO2 laser surgery: a larynx preservation alternative for selected hypopharyngeal carcinomas. *Head Neck*. 2004;26(11):953–959.

[25] Bernal-Sprekelsen M, Dazert S, Sudhoff H, Blanch JL, Vilaseca I. Complications of transoral laser surgery for malignant tumors of the larynx and hypopharynx [in German]. *Laryngorhinootologie*. 2009;88(1):28–34.

[26] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19):1945–1952.

[27] Bernier J, Cooper JS. Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? *Oncologist*. 2005;10(3):215–224.

[28] Yao M, Nguyen T, Buatti JM, et al. Changing failure patterns in oropharyngeal squamous cell carcinoma treated with intensity modulated radiotherapy and implications for future research. *Am J Clin Oncol*. 2006;29(6):606–612.

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ORIGINAL ARTICLE

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Transoral laser microsurgery for treatment of oropharyngeal cancer in 368 patients

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Abstract

Background: Oncological and functional outcome of transoral laser microsurgery (TLM) for primary treatment of oropharyngeal cancer was examined using a multimodal treatment concept.

Methods: A total of 368 patients with oropharyngeal squamous cell carcinoma (pT1-4, pN0-2, M0) underwent TLM +/− neck dissection (85%), +/− (chemo) radiotherapy (57%). The majority of patients had advanced stage III and IVa disease (79%).

Results: Five-year Kaplan-Meier estimates for local control were 83.5% for pT1, 74.1% for pT2, 77.3% for pT3, and 76.0% for pT4a tumors. Five-year estimates of overall, disease-specific, and recurrence-free survival for stage I were 76.0%, 92.8%, and 69.1%; for stage II 71.1%, 85.7%, and 49.6%; for stage III 61.7%, 72.5%, and 58.8%; and for stage IVa 57.3%, 73.7%, and 63.9%, respectively. Postoperative (chemo)radiotherapy improved the outcome for advanced disease. p16-positive tumors had superior survival estimates. Overall, 93.5% maintained regular oral nutrition without feeding tube dependency.

Conclusion: Primary TLM in multimodal concepts of treatment offers good oncologic outcome even for advanced-stage oropharyngeal cancer.

KEYWORDS

carbon dioxide laser, multimodal treatment concepts, oropharyngeal squamous cell carcinoma, oropharynx, transoral laser microsurgery (TLM)

1 | INTRODUCTION

Oropharyngeal cancer makes up 11.3% of all head and neck malignancies.[1] Squamous cell carcinoma (SCC) is the most common histological type.[1] Besides the most common risk factors, alcohol and tobacco consumption,[2] a geographical differing increase of association with human papillomavirus (HPV) infection has been observed.[3-7] The immunohistochemical detection of diffuse expression of the protein p16

Abbreviations: AJCC, American Joint Committee on Cancer; (C)RT, (chemo)radiotherapy; DSS, disease-specific survival; HPV, human papillomavirus; LCR, local control rate; ND, neck dissection; OS, overall survival; RFS, recurrence-free survival; SCC, squamous cell carcinoma; TLM, transoral laser microsurgery; TORS, transoral robotic surgery; UICC, Union International Contre le Cancer.

Bernhard G. Weiss and Friedrich Ihler contributed equally to this study.

was shown to correlate with an HPV infection, and therefore is used as a surrogate marker to be indicative for tumor's association with oncogenic HPV infection.[8,9]

Treatment of oropharyngeal cancer often requires a multimodal approach, consisting of surgery, chemotherapy, and radiotherapy. Curative treatment strategies are limited to surgery or primary (chemo)radiotherapy ((C)RT). Different approaches for surgical treatment of oropharyngeal cancer exist, including transoral or conventional open surgery. If indicated, surgical treatment is accompanied by unilateral or bilateral neck dissection (ND) and/or postoperative (C)RT. Transoral CO_2-laser microsurgery (TLM), originally introduced by Strong and Jako for the treatment of small laryngeal lesions,[10] was developed further by Steiner and colleagues to be used for the treatment of small and large tumors in multiple regions of the upper aerodigestive tract.[11-16]

The aim of this retrospective study is to assess the oncological and functional outcome of TLM +/− ND +/− postoperative (C)RT for treatment of oropharyngeal cancer and to compare this treatment strategy with common other multimodal treatment concepts described in literature. Another purpose was to address the prognostic impact of p16-positive carcinomas and to investigate the impact of postoperative (C)RT on oncologic outcome.

2 | PATIENTS AND METHODS

2.1 | Patients

We retrospectively reviewed the medical records and our hospital's cancer database of 368 patients who underwent elective TLM for SCC of the oropharynx at the Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Göttingen, between October 1986 and October 2015. Data were analyzed anonymously. Formalin-fixed paraffin-embedded tissue of patients who had received treatment after 2000 was analyzed for p16 expression. This study was approved by the institutional review board (Ethikkommission der Universitätsmedizin Göttingen) according to national regulations on February 29, 2016 (file reference number 10/2/16An). Written informed consent for anonymized analysis of their individual data was obtained from all patients prior to treatment at the University Medical Center Göttingen.

Patients with previously untreated SCC of the oropharynx (T1-4a, N0-2, M0) who underwent TLM with curative intent were included in the study. Tumors were staged according to the 7th edition of classification of the Union International Contre le Cancer (UICC)[17] and the American Joint Committee on Cancer (AJCC).[18] For functional or technical reasons, contraindications for TLM included extensive spread with involvement of the Eustachian tube or invasion of the carotid sheath. Moreover, TLM was unsuitable for cases for which access to the tumor was insufficient, for example, when there was extensive vertebral fixation or trismus. Six hundred and six patients were excluded from this study, such as patients with oropharyngeal cancers other than SCC (n = 53), patients who had suffered from previous primary tumor elsewhere (n = 120), patients with multiple primary synchronous malignant tumors (n = 71), patients who had either N3 neck disease (n = 85), simultaneous distant metastases (n = 25), recurrent disease of oropharyngeal malignancies treated elsewhere primarily (n = 35), started their primary therapy elsewhere (n = 11) or underwent primary (C)RT (n = 174), conventional surgery (n = 7), lateral pharyngotomy combined with or without TLM followed by flap reconstruction (n = 17) or lateral pharyngotomy with TLM (n = 4), or palliative treatment (n = 4). Age was not an exclusion criterion for surgery with curative intent.

2.2 | Staging procedures

Preoperative staging to evaluate tumor burden and to detect regional and distant metastases or synchronous primary tumors were performed as previously described.[19] Moreover, prior to planned surgery, a panendoscopy was performed under general anesthesia to assess the extent of the primary tumor and to select patients for TLM.

2.3 | Treatment of primary tumors

TLM was performed with a CO_2-laser in continuous superpulse mode. Resections were done using the technique described by Steiner.[11,20,21] In brief, TLM involves a step-by-step resection with cutting through the tumor, if necessary, allowing the surgeon to inspect the boundary between normal and abnormal tissue under microscopic magnification in a more accurate way compared to conventional surgery. Thus, the surgeon is able to preserve as much healthy tissue as possible and to inspect the depth of tumor invasion intraoperatively. Optimal visualization is achieved using different tongue depressors, retractors, or closed and distending laryngo-pharyngoscopes. Protrusion of the tongue base into the line of vision can be prevented by using a distending pharyngoscope with lateral wings. Furthermore, the differentiation between tumor and healthy tissue is possible by evaluating the lasers' cutting characteristics (eg, carbonization) under microscopic magnification. An appropriate resection margin of at least 5 mm could be maintained, if possible 10 mm. In certain cases of very large tumors, it was not possible to adhere to 5-10 mm margins. Concerning those cases, sampling from the tumor bed for frozen sections analysis ensured the R0 resection status. Decision for sampling from the tumor bed was decided by the surgeon and not necessarily limited to extended tumors. Evaluation of frozen sections required particular attention at the tongue base, since the lingual tonsil tissue makes intraoperative differentiation between tumor and healthy tissue more difficult. Here, not only tumor

tissue but also normal tissue showed increased carbonization as a result of the high tissue density, lymphatic tissue, and fibrosis. In every situation of piece-meal dissection for histological assessment accurate mapping, sometimes staining at the deep surface for orientation of deeper specimens and a close dialogue with the pathologist is essential. If final histology revealed margins less than 3 mm, the indication for a re-resection based on the high risk of submucosal tumor growth and low risk of functional impairment was generously performed. It is one advantage of TLM that it can be easily repeated if inadequate resection margins are found postoperatively. The impact of revision surgery on oncologic outcome was analyzed previously.[22]

2.4 | Histological assessment

Specimens of the primary tumors were routinely examined in a hematoxylin-eosin staining. Vertical 3-4 μm sections were stained in order to confirm diagnosis and resection margins. ND specimens were routinely investigated for nodal involvement.

Especially in the early years, molecular diagnostics of HPV status or p16 expression were not routinely performed. Therefore, a subgroup of patients treated in the period between the years 2000 and 2015 was chosen in order to evaluate the expression of the p16 protein. In 125 of 161 cases treated within this period, sufficient formalin-fixed paraffin-embedded tissue of the oropharyngeal primary tumor was available for p16 immunohistochemistry. Monoclonal p16 antibodies (p16 [JC8]: sc-56330, Santa Cruz Biotechnology, Inc., Dallas, Texas) (1:50; pH 9) were used in combination with diaminobenzidine (Dako, Agilent Technologies, Inc., Santa Clara, California) and the EnVision Flex+ System (Dako, Agilent Technologies, Inc.). Strong diffuse (≥75%) nuclear as well as cytoplasmic p16 immunostaining was considered positive, whereas no, weak, or moderate staining was classified as p16 negative.[8,9]

2.5 | Treatment of the neck

Patients were assessed for potential metastatic lymph node involvement as described previously.[19] In selected cases of patients with small tumors and clinically unsuspicious lymph nodes, a "wait-and-see" strategy was chosen. Follow-up commenced early following primary treatment and continued every 3 months with ultrasound scans of the neck. If the patient was seen with extended local disease (cT3-4a), the tumor infiltration depth exceeded 3 mm or if preoperative imaging revealed suspicious lymph nodes, a ND was performed. In cN0 cases, it was done as a selective ND which included levels II-IV. In cN + cases, a selective ND with levels II-IV, also including affected levels and/or structures as determined by imaging as well as intraoperatively, was performed. Bilateral NDs were carried out if imaging revealed suspicious lymph nodes bilaterally, or the primary tumor had an advanced stage with midline localization.

2.6 | Postoperative (C)RT

Postoperative (C)RT was mainly performed in cases of advanced neck disease (pN2a/b/c) or when the histopathological examination revealed extranodal extension and/or lymphatic invasion. From 1986 to 2015, the advancement of our understanding of the pathogenesis of cancer contributed to the development of more standardized recommendations for (C)RT. In accordance with this and the further development of radiooncology, different techniques and therapy schemes were used as previously described.[13]

2.7 | Follow-up

Patients underwent follow-up as previously described.[19] After 5 years without recurrences, a patient was considered as cured. It is worth mentioning that for many patients (47%), follow-up examinations continued for more than 5 years.

2.8 | Statistical methods

Regarding descriptive analysis, the mean value with corresponding SD, median, or frequencies with corresponding proportions in percentages were chosen in order to illustrate the respective outcome value. Postoperative follow-up data were available of all patients. Recurrence was defined as the same disease entity occurring >3 months after completed initial surgery. In contrast, disease occurring <3 months was considered as residual tumor. Late metastasis was defined as a lymph node disease occurring >3 months after initial clinical or histological negative neck (cN0/pN0), whereas recurrent metastasis occurred >3 months after the initial surgical treatment of patients with a histological confirmed neck disease (pN+). In order to compare survival rates across different groups, the method of Kaplan-Meier with a 95% confidence interval was used.[23] The assessed end points were overall survival (OS), disease-specific survival (DSS), recurrence-free survival (RFS), and the rate of local control (LCR). Interval calculation started at the date of primary surgery. Regarding the calculation of OS, events were defined as the date of death from all possible causes and censored observations as the date of last contact for alive patients. In disease-specific survival, events accounted exclusively for death from pharyngeal cancer. Referring to RFS, events were defined as local and regional recurrences, distant metastasis, and death due to primary disease, whereas any other causes of death not related to the primary disease, death due to second primary tumors, and patients alive without recurrences were counted as

censored observations. Calculating the LCR, local recurrences were considered as events. Accordingly, patients being alive without local recurrences or death regardless of reason were defined as censored observations. Statistical differences between groups were calculated by the log-rank test. A value of $P < .05$ was considered statistically significant. Analysis was performed using the software Dell Statistica Version 12 (Dell Inc., Round Rock, Texas).

3 | RESULTS

3.1 | Patients and therapy

A total of 368 patients diagnosed with oropharyngeal cancer met the inclusion criteria (72 women [19.6%], 249 men [80.4%], 1:3.5). The site of origin of oropharyngeal tumors that spread to adjacent regions, for example, epipharynx or hypopharynx, was classified accordingly by the operating surgeon. Thirty-five percent of oropharyngeal tumors were localized in the tonsils (n = 130), 24% in the tongue base (n = 89), 11% soft palate (n = 42), 9% vallecula (n = 34), 6% posterior wall (n = 22), 4% lateral wall (n = 15), 4% glossotonsillar sulcus and palatal arch (n = 14), 6% uvula (n = 21), and <1% in the tonsillar fossa (n = 1). Mean age at diagnosis was 57 ± 10 years (range, 29-91 years). Nine percent of patients had UICC stage I disease (n = 33), 12% stage II (n = 45), 22% stage III (n = 82), and 57% stage IVa (n = 208). Distribution of T and N categorization is shown in Table 1.

Thirty-seven patients were exclusively treated by laser surgery (10%), 124 had TLM combined with unilateral or bilateral ND (34%). The majority of patients received multimodal treatment. Fifty-two percent of patients were treated by TLM and ND, followed by (C)RT (191 patients), and 4% had TLM and postoperative (C)RT without ND (n = 16). Of the 207 patients (56%) receiving postoperative radiotherapy, in 27% (99 cases) it was combined with chemotherapy. ND was performed in 315 patients (86%), a unilateral dissection in 52% (n = 165), and a bilateral dissection in 48% (n = 150). The majority of cases were done by selective ND, levels II and III were included in all but 6 cases (1%). Additionally, level I (n = 103), and/or level IV (n = 164), and/or level V (n = 98) were completed in 365 (78%) of 465 neck sides. Modified radical ND was performed in 5 (1.1%) and radical ND in 8 (1.7%) cases. Two hundred and twenty six patients (61%) had positive lymph nodes, out of which 33 patients (9%) had bilateral disease. Extranodal extension occurred in 84 cases (22.8%).

Mean time until death (or lost to follow-up) was 69.6 ± 52.5 months with a maximum of 253 months.

3.2 | Oncologic results

At the time of last follow-up of all 368 patients, 47.8% (n = 176) were still alive and free of disease, 1.1% (n = 4) were living with tumor, 16% (n = 59) had died by other causes not related to the primary disease, 21.5% (n = 79) had died from disease, and 13.6% (n = 50) had died due to a second primary tumor. Twenty-nine percent of cases had disease recurrence (n = 107). Local recurrence appeared in 16% (n = 58), locoregional in 4% (n = 14), were late nodal metastasis in 5% (n = 19), and in 4% (n = 16) recurrent nodal metastasis. In summary, 72 cases (20%) had local or locoregional recurrences. The 5-year LCR after TLM is shown in Figure 1 and Table 2, pT-category related.

Second primary tumors developed in 90 (24%) of all 368 patients. In 48%, these tumors were located in the ear, nose, and throat area (n = 43). Other primary sites included the lung (22%; n = 20), esophagus (8%; n = 7), gastrointestinal tract (8%; n = 8), urogenital system (6%; n = 5), and others (9%; n = 8).

Figure 2 depicts stage-related OS, DSS, and RFS for all the 368 cases. Table 2 shows oncological results for patients with oropharyngeal cancer in total, stage, and pT-category related.

In order to analyze the influence of postoperative (C)RT, a subgroup of 290 patients with advanced disease (pT3-4 and/or pN+) was defined. Here, 97 patients, who did not receive postoperative (C)RT, were compared to 193 patients, who were treated postoperatively with (C)RT. Those who received postoperative (C)RT had a significant higher outcome in the estimates for RFS ($P = .001$) as well as local control ($P = .004$) (Table 3 and Figure 3).

In order to analyze the association between HPV infection and oncological outcome in patients who had primary surgical treatment by TLM, a subgroup of patients treated

	c/pN0		pN1		pN2a		pN2b		pN2c		Total	
pT1	33	9%	14	4%	4	1%	17	5%	2	1%	70	19%
pT2	45	12%	20	5%	3	1%	40	11%	7	2%	115	31%
pT3	37	10%	13	4%	2	1%	36	10%	11	3%	99	27%
pT4a	27	7%	13	4%	5	1%	26	7%	13	4%	84	23%
Total	142	39%	60	16%	14	4%	119	32%	33	9%	368	100%

TABLE 1 Distribution of T and N categorization. Number and percent from grand total

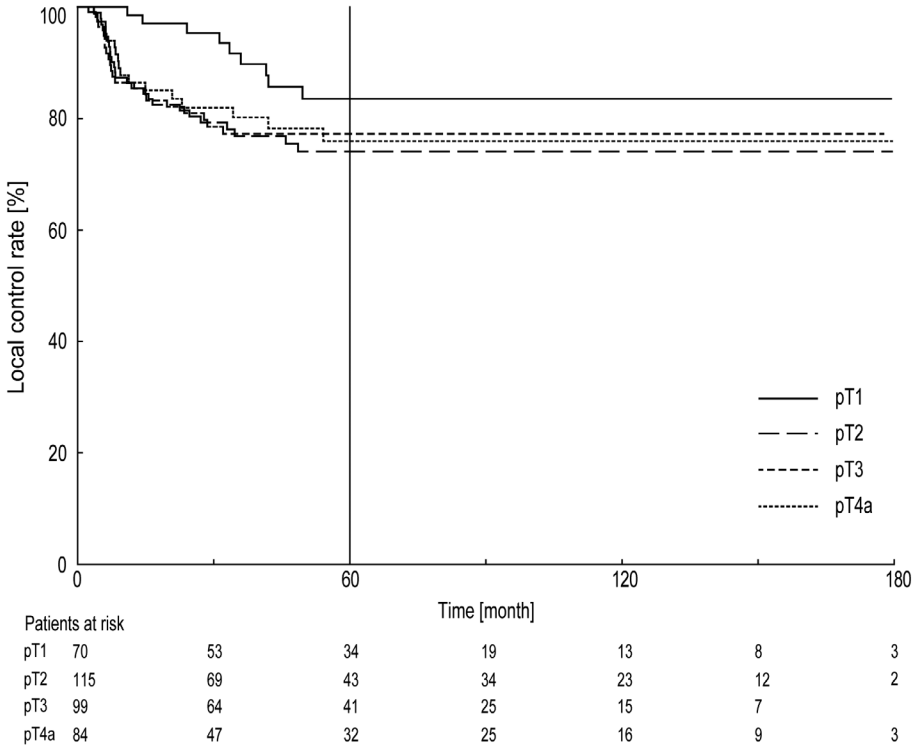

FIGURE 1 Five-year Kaplan-Meier estimates for local control related to pT category. Patients at risk are shown below the diagram

TABLE 2 Five-year oncologic results (in percent) for 368 patients with oropharyngeal cancer stage and pT-category related

	I	pT1	II	pT2	III	pT3	IVa	pT4a	I-IVa	pT1-pT4a
OS	76.0	68.5	71.1	60.0	61.7	62.4	57.3	56.5	61.5	61.5
DSS	92.8	85.1	85.7	74.3	72.5	72.7	73.7	77.0	76.5	76.5
RFS	69.1	67.5	49.6	54.7	58.8	64.8	63.9	61.0	61.3	61.3
LCR	77.7	83.5	63.7	74.1	74.1	77.3	82.0	76.0	77.2	77.2

Abbreviations: DSS, disease-specific survival; LCR, local control rate; OS, overall survival; RFS, recurrence-free survival.

from 2000 to 2015 was investigated. Immunohistochemistry for p16 was performed on 125 out of 161 oropharyngeal tumor samples. Of these, 44% (n = 55) showed diffuse p16 immunostaining and were classified as p16-positive oropharyngeal cancers. In contrast, 56% (n = 70) of these tumors showed moderate, weak, or no staining at all and were classified as p16 negative. Patients' characteristics, T and N status as well as UICC stages and data regarding treatment modalities and recurrences of this subgroup are summarized in Table 4. Survival estimates were analyzed for stage III/IV p16 positive (n = 50) and negative (n = 52) cases. Patients suffering from p16-positive carcinoma had a significant better OS (P = .02) and increased values of DSS and RFS (Table 5 and Figure 4).

3.3 | Postoperative management and complications

Nasogastric feeding tubes were placed in cases with locally advanced cancers in order to reduce the risk of aspiration pneumonia. A nasogastric feeding tube was postoperatively placed in 67% of patients (n = 245) to maintain oral nutrition during the course of wound healing. The median duration of placement was 8.5 days with a range of <1-131 days. In 13% (n = 48), gastrostomy tubes had to be placed due to severe dysphagia and recurrent aspiration after surgery or (C)RT without sufficient improvement. Out of 48 patients with gastrostomy tubes, 87.5% (n = 42) received postoperative (C)RT. Sixteen patients a pT4a, 15 a pT3, 14 a pT2, and 3 a pT1 tumor. Twenty-four patients (6.5%) only required a temporary gastrostomy tube which was removed after a median duration of 5.2 months (range, <0.4-26.1 months). The remaining 24 patients (6.5%) had the permanent tube until death or lost to follow-up. Nasogastric feeding tubes and gastrostomy tubes were removed when patients were able to take food orally and showed no clinical or radiological signs of aspiration.

A tracheotomy was necessary in 14 cases (3.8%). Six patients had a tracheotomy placed preoperatively or intraoperatively, five patients received it within 30 days after

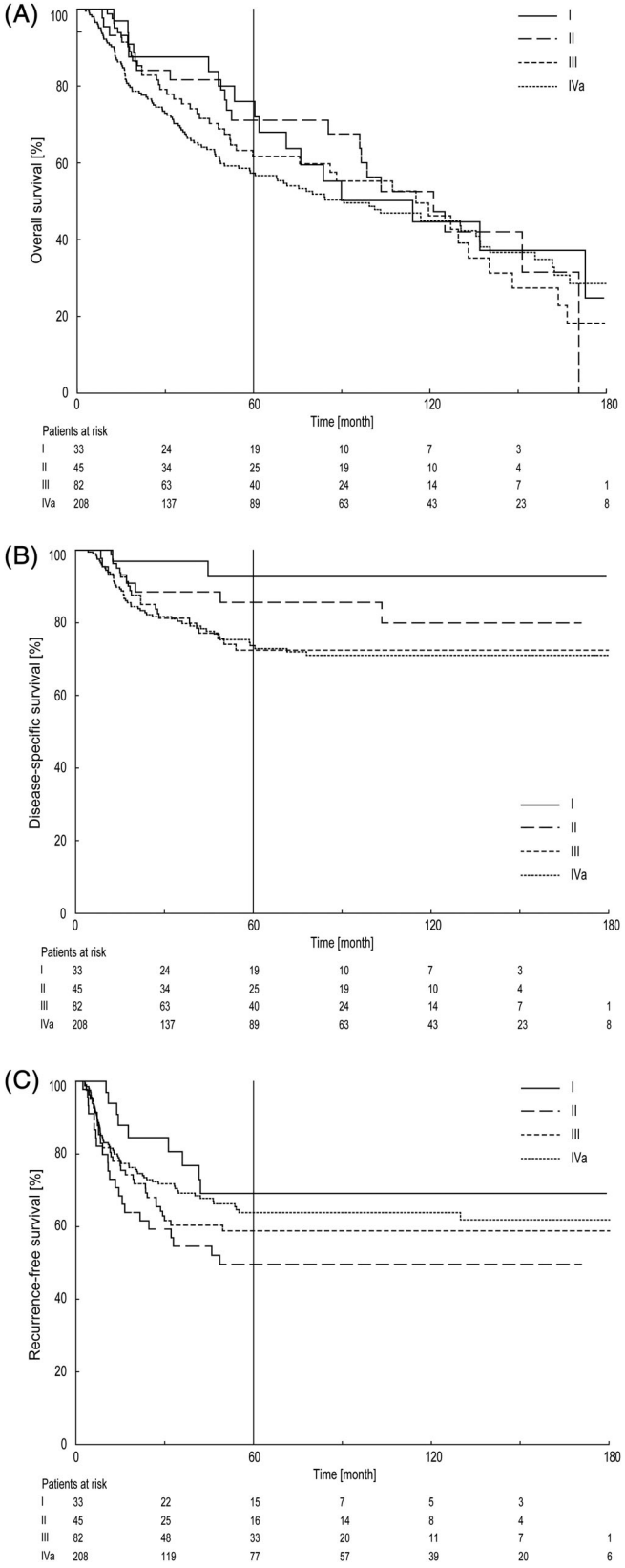

FIGURE 2 Five-year Kaplan-Meier estimates for A, overall; B, disease specific; and C, recurrence-free survival stage related for 368 patients with oropharyngeal cancer. Patients at risk are shown below the diagrams

TABLE 3 Distribution of 290 patients with advance disease and indication or recommendation for postoperative (chemo)radiotherapy ((C)RT) (pN+; pT3-4)

	III + IVa	pT3 + pT4a
(C)RT yes	193	119
(C)RT no	97	64
P value LCR	**.004**	**.007**
P value RFS	**.001**	**.009**

Notes: The group receiving postoperative (C)RT exhibited significant superior estimates for 5-year local control rate (LCR) and recurrence-free survival (RFS) compared to those without this adjuvant therapy. The *P* values for LCR and RFS comparing the group actually receiving (C)RT and the group that did not (significant *P* values in bold).

surgery following postoperative complications such as bleeding or edema. A further two patients required a tracheotomy after the start of (C)RT.

Postoperative complications and corresponding management are summed up in Table 6.

4 | DISCUSSION

Oropharyngeal cancers are managed primarily by surgery such as conventional open surgery or transoral approaches including TLM or, more recently, robotic surgery. If indicated, surgical treatment is accompanied by ND and (C)RT. Alternatively, these patients can be treated with primary (C)RT. Comparison of different treatment strategies is difficult due to the lack of randomized controlled trials. Moreover, different stages, end points, observation periods, statistics, and indication criteria for diverse treatment modalities make it even more complicated to compare the effectiveness of one treatment over the other. The aim of this study was to assess TLM for primary management of early and advanced carcinomas of the oropharynx, paying particular attention to multimodal treatment concepts. Furthermore, we wanted to investigate the prognostic impact of p16-positive carcinomas.

To the best of our knowledge, this is the largest cohort of patients with oropharyngeal cancers treated surgically and exclusively by TLM (+/− ND +/− (C)RT). TLM has become the principal treatment strategy for pharyngeal cancers in many centers. Thus, over the last decade, groups published their results and long-time oncologic outcome.[24-29] Here, we calculated the survival rates for all stages and pT categories to allow comparison to other published studies. In our study, the 5-year DSS decreased from 92.8% for stage I to 73.7% for stage IVa disease. Our results were comparable to other studies.[24-29] However, Haughey et al observed relatively high survival rates (84% DSS for advanced stage

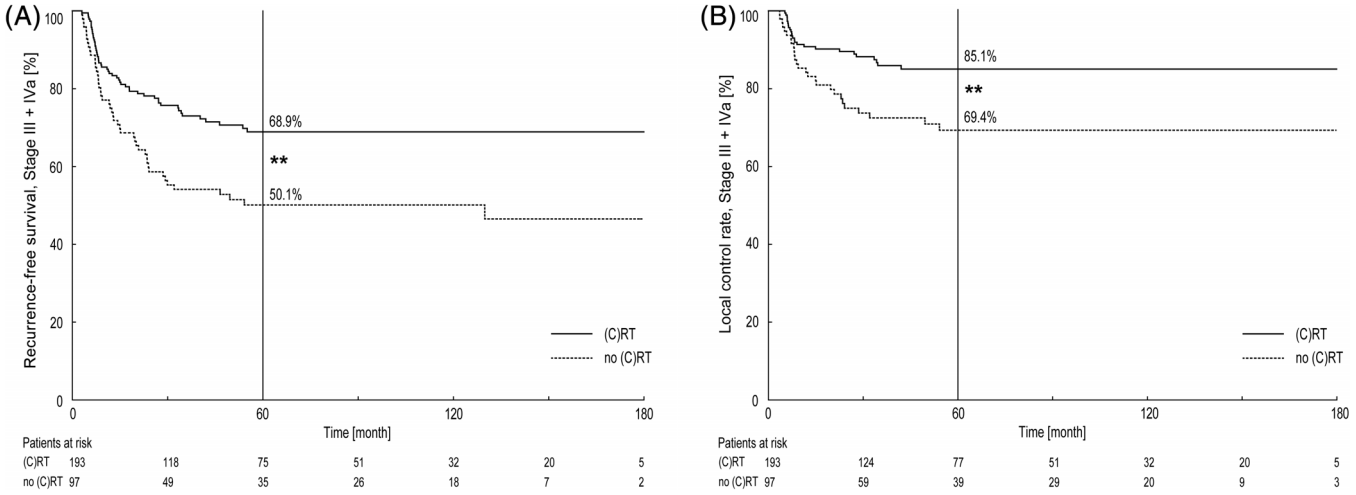

FIGURE 3 Five-year Kaplan-Meier estimates for A, recurrence-free survival of stages III-IVa and B, local control of stage III-IVa for 290 patients with the indication or recommendation for postoperative (chemo)radiotherapy ((C)RT) that received or did not receive this adjuvant treatment modality. $^{**}P < .01$, (C)RT. Patients at risk are shown below the diagrams

cancer, III-IV) for a cohort of oropharyngeal cancer with a large proportion of p16 and HPV positive cases.[26]

HPV-related (p16 positive) carcinomas are associated with a more favorable prognosis compared to the high-risk situation of HPV-negative tumors of smokers.[30] In our study, we looked at patients with oropharyngeal cancer who were treated between 1986 and 2015. A proportion of cases between 2000 and 2015 was evaluated for p16 expression by immunohistochemistry followed by analysis of their oncologic outcome. Patients with p16-positive carcinomas had a better OS and showed clear trends toward an improved DSS and RFS compared to p16-negative cases. Our results are in agreement with similar results published by various groups that oropharyngeal carcinomas with a positive p16 status have a more favorable prognosis compared to p16-negative ones (present study stage III/IVa cases: OS: 83% vs 63%, DSS: 85% vs 71%, RFS: 77% vs 62%).[25,26,31,32] Furthermore, the oncological results of the studies' p16-positive subgroup are comparable to those studies that include a high rate of p16-positive oropharyngeal cancers.[25,26,31,33,34] In contrast, the survival estimates for the complete study group are comparable to those studies that do not give information about the carcinomas' p16 status.[24,27,29,31] Consequently, in order to compare the survival data of different therapy regimes for oropharyngeal cancer, the proportion of p16-positive tumors needs to be taken into account.

Most of the recent studies report relatively high rates of p16-positive carcinomas or focus solely on p16-positive ones. In contrast, studies with a sufficient cohort size that define and analyze exclusively p16-negative oropharyngeal carcinomas are rarely available. However, in our German subgroup, the proportion of p16-negative cases is 56%, which enabled us to provide detailed data not only on p16 positive, but also on p16-negative tumors. Hence, the present study provides long-term oncological outcome data derived from the largest group of uniformly treated homogenous p16-negative oropharyngeal tumors that is currently available in the literature. An overview about the oncological results of the present study and the current literature with, if reported, the p16 status is provided in Table 7.

The distinction between p16-positive and negative tumors was introduced in the new 8th UICC and AJCC[9] edition of cancer staging system. To date, it has not yet resulted in different standard treatment strategies.[41] By applying the 7th edition of UICC[17] and AJCC[18] cancer staging, we ensure optimal comparison to results from similar studies published so far (Table 7).

TLM is a long-time standard in many centers for minimally invasive transoral surgery for oropharyngeal tumors. Transoral robotic surgery (TORS) on the other hand is a relatively novel minimally invasive technique which is still under development. Advantages of this technology, especially for tongue base tumors, are due to three-dimensional view on the operation site. One study analyzed a cohort of 314 patients with tonsillar and base of tongue cancer treated by TORS + ND +/− (C)RT. By looking at 86.9% T1-2 and 91.1% HPV/p16-positive tumors, a 5-year DSS rate of 94%[33] was comparable with TLM (Table 7). The same authors addressed the need for tracheotomies or gastrostomy tubes in a similar study, which included the 3-year oncological results after TORS-based treatment.[35] A temporary tracheotomy was placed in 25.8% and a gastrostomy tube was necessary in 27.3%.[35] Considering the high number of pT1-2 oropharyngeal carcinomas (84.8%), these rates of tracheotomies and gastrostomy tube dependency seem relatively high compared to our cohort. Our study included 50%

TABLE 4 Subgroup of 125 patients[a] with p16-positive and negative tumors treated between 2000 and 2015. Characteristics, T and N categorization, and tumor classification (UICC)

		p16 positive (n = 55)		p16 negative (n = 70)	
		Number	**Percent**	**Number**	**Percent**
Age (y)	Mean	58.5		57.4	
	SD	11.1		8.9	
	Range	29-91		40-76	
Sex	Female	12	21.8	13	18.6
	Male	43	78.2	57	81.4
T categorization	pT1	8	14.5	12	17.1
	pT2	23	41.8	18	25.7
	pT3	18	32.7	23	32.9
	pT4a	6	10.9	17	24.3
N categorization	c/pN0	10	18.2	29	41.4
	pN1	12	21.8	10	14.3
	pN2a	2	3.6	1	1.4
	pN2b	26	47.3	22	31.4
	pN2c	5	9.1	8	11.4
Tumor classification (UICC)	I	0	0.0	9	12.9
	II	5	9.1	9	12.9
	III	14	25.5	15	21.4
	IVa	36	65.5	37	52.9
Treatment	TLM	2	3.6	10	14.3
	TLM + ND	16	29.1	19	27.1
	TLM + ND + RT	13	23.6	16	22.9
	TLM + ND + (C)RT	23	41.8	23	32.9
	TLM + RT	1	1.8	1	1.4
	TLM + (C)RT	0	0	1	1.4
Recurrences	Local	5	9.1	12	17.1
	Locoregional	1	1.8	1	1.4
	Regional	3	5.5	6	8.6

Abbreviations: (C)RT, (chemo)radiotherapy; ND, neck dissection; RT, radiotherapy; TLM, transoral laser microsurgery; UICC, Union Internationale Contre le Cancer.

[a]Cases with sufficient formalin-fixed paraffin-embedded tissue available.

extended pT3-4a tumors and 3.8% of all 368 patients required a tracheotomy. They were predominantly placed within 30 days after initial surgical treatment, when complications, mostly postoperative bleeding, occurred. Furthermore, a temporary gastrostomy tube was placed in 13% of all patients. The current studies describing TORS for oropharyngeal cancer lack this information.[32,33]

One advantage of TLM is a low complication rate. In our study, the most common complications was postoperative bleeding that occurred in 11% (n = 42). The majority of cases were managed by transoral electrocautery or clipping. This is in line with the results of other studies investigating TLM for oropharyngeal cancer.[25,27,28] Especially large tumors (T3-4) have a significant higher risk for complications.[42] This was also observed in our cohort, in which 65.9% of complications occurred in pT3-4 cases.

Another advantage of TLM included minimal trauma to healthy tissue due to the transoral approach and the microscopic view of the operation site with the ability to differentiate between tumor and healthy tissue. In contrast, during conventional surgery, there is often need for more invasive

TABLE 5 Five-year oncologic results (in percent) for a subgroup of 102 patients with advance disease (stages III and IVa) and p16-positive or negative oropharyngeal cancer

	p16 positive and negative (n = 102)	p16 positive (n = 50)	p16 negative (n = 52)	*P* value
OS	73.3	83.2	63.1	**.02**
DSS	78.3	84.9	71.3	.075
RFS	69.9	77.2	62.5	.09
LCR	85.6	89.5	82.4	.17

Note: Significant *P* values in bold.
Abbreviations: DSS, disease-specific survival; LCR, local control rate; OS, overall survival; RFS, recurrence-free survival.

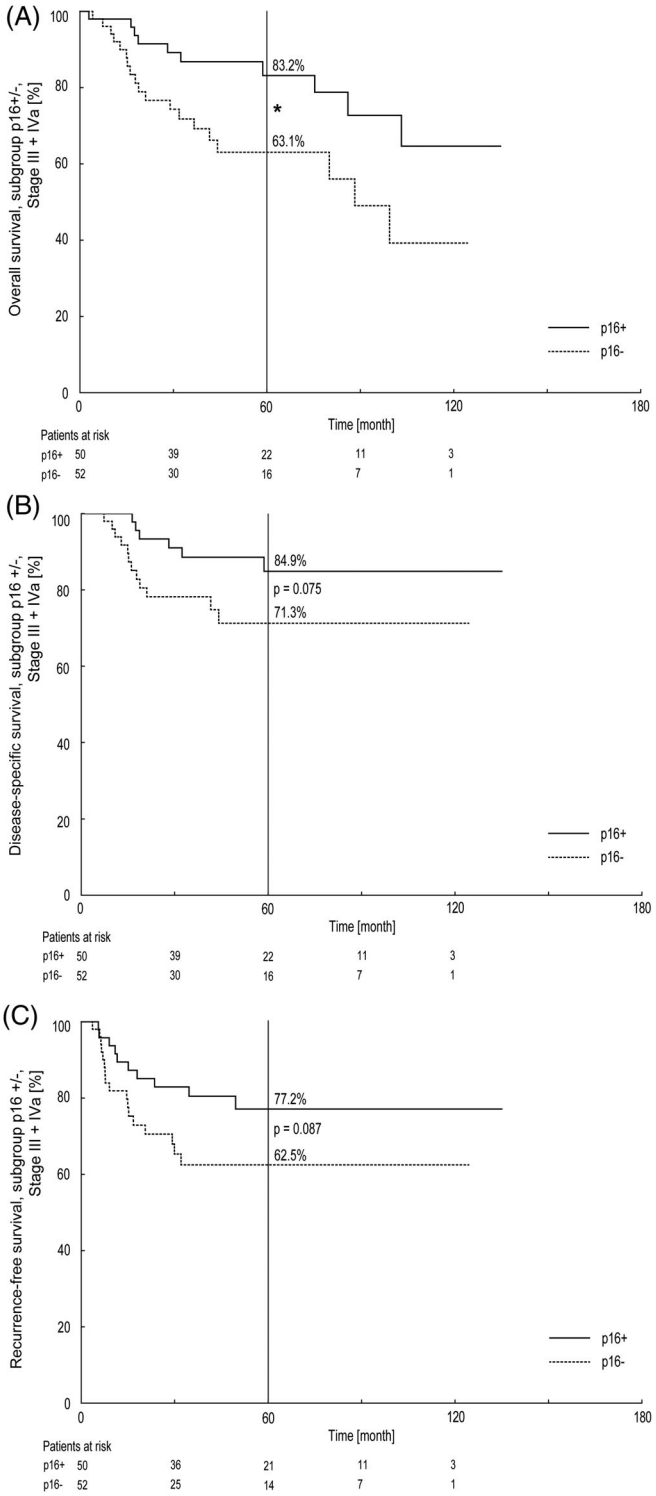

FIGURE 4 Five-year Kaplan-Meier estimates for A, overall survival of stage III - IVa; B, disease-specific survival of stage III - IVa; and C, recurrence-free survival of stage III - IVa for 102 patients with advanced disease and p16-positive or p16-negative carcinomas. *$P < .05$. Patients at risk are shown below the diagrams

approaches to access the tumor site. Even though small tumors can also be resected transorally by conventional lateral oropharyngectomy,[36,37] larger tumors treated by conventional surgery may require open approaches like a lipsplit with mandibulotomy, if necessary followed by reconstruction.[36] Rahmati et al looked at T1-4 tumors treated by different conventional surgical approaches such as transoral surgery, open surgery via mandibulotomy, or composite resection (mandibulectomy). In 55% of cases, tumor resection was followed by flap reconstruction.[31] Oncological outcome of these alternative surgical approaches is comparable to TLM (Table 7) that is, if necessary, suitable for subsequent reconstructions as well. Options for the treatment of large pharyngeal defects include, for instance, the radial forearm free flap, the pectoralis major myocutaneous flap, or the supraclavicular artery island flap.[43-45]

An alternative to surgical treatment is primary (C)RT, followed, if necessary, by salvage surgery.[39,40] Primary (C)RT is also the only curative option for non-resectable oropharyngeal tumors. In comparison with radiotherapy alone, concomitant (C)RT resulted in an improved oncological outcome as shown in a phase III multicenter randomized trial for patients with advanced-stage oropharyngeal cancer (5-year OS of 22% vs 16% and locoregional control of 48% vs 25%).[38] Compared to primary surgery, one needs to consider the long-term toxicity in primary radiotherapy-based treatment strategies. Whereas in earlier years, the occurrence of 9%-16% severe late toxicity was reported for cohorts treated between 1964 and 2003 (eg, osteonecrosis, orocutaneous fistula, fatal radiation-induced sarcoma, soft tissue necrosis, and chondronecrosis necessitating a total laryngectomy),[39,40] more recent data reported 1.2%-2% grade 4 toxicities[38] according to the RTOG/EORTC scale.[46] Moreover, the current technique of intensity-modulated radiation therapy needs to be considered as a better alternative which is much less toxic. Modern techniques and protocols of (C)RT aim to achieve best tumor control and to minimize treatment-related toxicity by maximal sparing of healthy

TABLE 6 Postoperative complications and corresponding management

	Total (n = 368)		pT1-pT2 (n = 185)		pT3-pT4 (n = 183)	
	Number	Percent	Number	Percent	Number	Percent
Bleeding, n = 42 (11%)						
Electrocautery/clipping	38	10.3	15	8.1	23	12.6
Ligation of a branch of the external carotid artery	4	1.1	0	0	4	2.2
Fistula formation, n = 1[a] (0.3%)						
Local muscle flap	1[a]	0.3	0	0	1[a]	0.5
Abscess formation, n = 1 (0.3%)						
Surgical drainage	1	0.3	0	0	1	0.5

[a]Occurred during initial tumor resection with simultaneous neck dissection.

tissue. An overview about the oncological results of primary (C)RT is given in Table 7.

Nowadays, in order to achieve optimal oncological as well as functional results, oncological centers design personalized multimodal treatment strategies based on individual patients' requirements in a multidisciplinary setting. These comprise the surgical aspects as well as (C)RT. After primary surgery, postoperative (C)RT is the standard treatment approach in cases of advanced tumor size pT3-4 and/or at least pN2 neck disease.[47,48] Nevertheless, it is still debated whether small tumors with a single lymph node metastasis (pT1-2 pN1) should receive postoperative radiotherapy. Therefore, a prospective randomized multicenter clinical trial is currently ongoing (ClinicalTrials.gov Identifier: NCT00964977). Patients in the present cohort received postoperative (C)RT mainly in case of advanced neck disease (N2a/b/c) or when the histopathological examination revealed extranodal extension and/or lymphatic invasion. However, the present study includes a large cohort of patients with advanced disease that did not receive postoperative (C)RT, based on the current state of knowledge they might today receive (C)RT. Thus, the current data provide the unique opportunity to directly analyze the impact of postoperative (C)RT on long-term survival within a patient cohort that will most likely not be available again. In this group of 290 patients with advanced disease, those who actually received (C)RT had a significant higher outcome in RFS as well as a significant superior local control. This corresponds to data by Haughey et al that radiotherapy after TLM reduced the risk of death and recurrence by >50% relative to receiving no postoperative treatment.[26] Moreover, concerning hypopharyngeal cancer, we previously demonstrated as well that postoperative (C)RT resulted in improved RFS and local control when following the present recommendation for this additional treatment modality.[19] Taken together, these results support today's guidelines for postoperative (C)RT being a useful additional treatment for advanced stage disease.

Even though 79% of cases in this study comprised advanced cancers (stage III/IVa), the multimodal treatment concepts that comprised TLM, often ND and in many cases postoperative (C)RT, resulted in a good functional outcome. This included the ability of oral alimentation with only 6.5% of all patients requiring a permanent gastrostomy tube and 6.5% requiring one only temporarily. In contrast, for primary (C)RT, it is frequently placed routinely and more often required permanently.[49,50]

Limitations of this study are the retrospective design. Additionally, no direct comparison to alternative strategies was possible as equally large patient cohorts were not available at our center. The strength is that this study presents not only the largest but also a very well characterized cohort of oropharyngeal cancer cases in literature so far. All cases were treated by a TLM-based concept.

Moreover, it comprises not only a very well-characterized subgroup of consistent p16 positive, but also an equally well-characterized subgroup of homogenous p16-negative oropharyngeal tumors. Therefore, it addresses the currently discussed impact of p16 status on prognosis. Furthermore, today's guidelines for postoperative (C)RT are supported by the direct comparison of patients with advanced disease, who did or did not receive this additional treatment.

In conclusion, we demonstrated that the TLM-based multimodal treatment concept with or without ND and, if necessary, subsequent (C)RT resulted in good oncological outcome even for advanced-stage oropharyngeal cancer. Treatment strategies should be determined in interdisciplinary conferences and compared in prospective randomized trials, also taking a patient's quality of life into account. Moreover, the demonstrated impact of p16 status on prognosis emphasizes the need to differentiate between these two subgroups in future investigations.

TABLE 7 Overview of studies evaluating different treatment strategies of patients with tumors of the oropharynx

Study	Treatment	No.	Follow-up	Comment	p16	UICC Edition	Stage (UICC)	TNM	OS (%)	DSS (%)	RFS (%)	LCR (%)
Present study, complete cohort[a]	1	368	5-y		15% p16+ 19% p16− 66% p16 N/A	7th (2009)	I-IV (79% III-IVa)	pT1-4	I = 76, II = 71, III = 62, IVa = 57; I-IVa = 62	I = 93, II = 86, III = 72, IVa = 74; I-IVa = 77	I = 69, II = 50, III = 59, IVa = 64; I-IVa = 61	pT1 = 84, pT2 = 74, pT3 = 77, pT4a = 76; pT1-4a = 77
Present study, p16 positive subgroup[b]	1	55	5-y		100% p16+	7th (2009)	II-IVa (91% III-Iva)	pT1-4 (44% pT3-4)	II = 100 III = 92, IVa = 80; II-IVa = 85; III-IVa = 83	II = 100 III = 92, IVa = 82; II-IVa = 86; III-IVa = 85	II = 53 III = 61, IVa = 84; II-IVa = 75; III-IVa = 77	pT1 = 86, pT2 = 83, pT3 = 88; pT4a = 100; pT1-4a = 86
Present study, p16 negative subgroup[b]	1	70	5-y		100% p16−	7th (2009)	I-IVa (74% III-IVa)	pT1-4	I = 86, II = 71, III = 66, IVa = 62; I-IVa = 67; III-IVa = 63	I = 86, II = 89, III = 66, IVa = 75; I-IVa = 76; III-IVa = 71	I = 63, II = 42, III = 53, IVa = 70; I-IVa = 59; III-IVa = 62	pT1 = 69, pT2 = 82 pT3 = 80, pT4a = 82; pT1-4a = 78
Rogers et al[29]	1	162	5-y	55% HPV+ 31% HPV− 14 % HPV N/A	p16 N/A	N/A	I-IV (54% IV)		68			
Karatzanis et al[27]	1	53	5-y		p16 N/A	6th (2002)		pT1 pN0-3		89		95
Iro et al,[28] complete cohort	1	134	5-y		p16 N/A	7th (2009)		pT1-2 pN0-pN+	60	79		89
Iro et al,[28] pT1 subgroup	1	59	5-y		p16 N/A	7th (2009)		pT1 pN0-pN+	74	86		92
Iro et al,[28] pT2 subgroup	1	75	5-y		p16 N/A	7th (2009)		pT2 pN0-pN+	48	72		87
Haughey et al[26]	1	204	5-y	62% HPV+ 22% HPV− 15% HPV N/A	82% p16+ 9% p16− 9% p16 N/A	N/A	III-IV	pT1-4	78	84	74	97
Rich et al,[25] complete cohort	1	84	5-y		82% p16+ 5% p16− 13% p16 N/A	N/A	III-IV	pT1-4 (74% T1-2)	88	92		
Rich et al,[25] p16 positive subgroup	1	69	5-y		100% p16+	N/A	III-IV	pT1-4 pN0-3	90	94		

(Continues)

TABLE 7 (Continued)

Study	Treatment	No.	Follow-up	Comment	p16	UICC Edition	Stage (UICC)	TNM	OS (%)	DSS (%)	RFS (%)	LCR (%)
Rich et al,[25] p16 negative subgroup	1	4	5-y		100% p16−	N/A	III-IV	pT2-3 pN1-3	25	50		
Grant et al[24]	2	44	5-y		p16 N/A p16 N/A	N/A	I-II III-IV (9% IV)	pT1-3 (20% pT3)	79 86	88 86		
Sinha et al[34]	3	20	5-y		95% p16+ 5% p16−	N/A		cT2-4b cN0-3	83	87		
Moore et al[35]	4	314	5-y	91% HPV/p16+ 7% HPV/p16− 2% HPV/p16 N/A	p16 N/A	7th (2009)	I-IV (9% III, 75% IVa, 6% IVb)	pT1-4 (87% T1-2)	86	94		
Park et al,[32] complete cohort	5	80	5-y		59% p16+ 41% p16−	7th (2009)	III-IV	pT1-4 N0-3 (64% T1-2)	89	90		
Park et al,[32] p16 positive subgroup	5	47	5-y		100% p16+	7th (2009)	III-IV	pT1-4 N1-2	93	93		
Park et al,[32] p16 negative subgroup	5	33	5-y		100% p16−	7th (2009)	III-IV	pT1-4 N0-3	86	89		
Moncrieff et al[36]	6	92	5-y		p16 N/A	N/A		pT1-2 pN0-3		83 (pT1 = 96, pT2 = 78)		87
Laccourreye et al[37]	7	166	5-y		p16 N/A p16 N/A	5th (1997)	I-IV (31% III-IV)	pT1-3, pN0-3	58			pT1 = 89, pT2 = 82, pT3 = 63; pT1-3 = 82
Rahmati et al,[31] complete cohort	8	88	5-y		55% p16+ 20% p16− 25% p16 N/A	N/A	I-V (14% III, 69% IV)	pT1-4 N0-N2 (75% pT1-2)	pT1 = 81, pT2 = 70, pT3 = 40, pT4 = 37; pT1-4 = 66	pT1 = 92, pT2 = 78, pT3 = 50, pT4 = 69; pT1-4 = 82		89
Rahmati et al,[31] p16 positive subgroup	8	48	5-y		100% p16+	N/A			74	89		

(Continues)

TABLE 7 (Continued)

Study	Treatment	No.	Follow-up	Comment	p16	UICC Edition	Stage (UICC)	TNM	OS (%)	DSS (%)	RFS (%)	LCR (%)
Rahmati et al,[31] p16 negative subgroup	8	18	5-y		100% p16−	N/A			47	66		
Denis et al,[38] primary RT subgroup	9	112	5-y		p16 N/A	N/A	III-IV	T1-4 N0-3	16	15		LRC: 25
Denis et al,[38] primary concomitant CRT subgroup	10	108	5-y		p16 N/A	N/A	III-IV	T1-4 N0-3	22	27		LRC: 48
Mendenhall et al[39]	11	503	5-y	100% tonsillar carcinomas	p16 N/A	6th (2002)	I-IV (19% III, 37% IVa 24% IVb)	T1-4 N0-3	I = 54, II = 61, III = 62, IVa = 57, IVb = 33; I-IV = 53	I = 100, II = 86, III = 84, IVa = 73, IVb = 46; I-IV = 72		T1 = 88, T2 = 84, T3 = 78, T4 = 61; T1-4 = 79
Mendenhall et al[40]	11	333	5-y	100% base of tongue carcinomas	p16 N/A	6th (2002)	I-IV (17% III, 37% IVa, 38% IVb)	T1-4 N0-3	I-II = 67, III = 66, IVa = 67, IVb = 33; I-IV = 54	I-II = 91, III = 77, IVa = 84, IVb = 45; I-IV = 68		T1 = 98, T2 = 92, T3 = 82, T4 = 53; T1-4 = 82

Notes: Follow-up in years; OS, RFS, DSS, LCR, and LRC rates in percentages. Treatment approaches: 1, transoral laser microsurgery (TLM) +/− neck dissection (ND) +/− (chemo)radiotherapy ((C)RT); 2, TLM +/− ND; 3, TLM +/− additional conventional transcervical tumor resection + pharyngotomy for further reconstruction +/− postoperative (C)RT; 4, TORS + ND +/− (C)RT; 5, TORS +/− ND +/− neoadjuvant chemotherapy +/− postoperative (C)RT; 6, conventional surgery (transoral or lipsplit mandibulotomy) +/− ND +/− (C)RT; 7, conventional surgery (transoral lateral oropharyngectomy) +/− ND +/− preoperative induction chemotherapy +/− RT; 8, conventional surgery +/− reconstruction +/− ND +/− RT; 9, primary radiotherapy; 10, primary concomitant chemoradiotherapy; 11, primary radiotherapy +/− (induction and/ or concomitant) chemotherapy +/− ND.
Abbreviations: DSS, disease-specific survival; HPV, human papillomavirus; LCR, local control rate; LRC, locoregional control; N/A, data not available; OS, overall survival; RFS, reccurrence-free survival; UICC, Union Internationale Contre le Cancer.

[a]Period of inclusion 1986-2015.

[b]Period of inclusion 2000-2015 (cases with formalin-fixed paraffin embedded tissue available).

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REFERENCES

1. Cooper JS, Porter K, Mallin K, et al. National Cancer Database report on cancer of the head and neck: 10-year update. *Head Neck*. 2009;31(6):748-758.
2. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev*. 2009;18(2):541-550.
3. Anantharaman D, Abedi-Ardekani B, Beachler DC, et al. Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. *Int J Cancer*. 2017;140(9):1968-1975.
4. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.
5. Wurdemann N, Wagner S, Sharma SJ, et al. Prognostic impact of AJCC/UICC 8th edition new staging rules in oropharyngeal squamous cell carcinoma. *Front Oncol*. 2017;7:129.
6. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-1956.
7. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. *J Clin Oncol*. 2015;33(29):3235-3242.
8. Quabius ES, Haag J, Kuhnel A, et al. Geographical and anatomical influences on human papillomavirus prevalence diversity in head and neck squamous cell carcinoma in Germany. *Int J Oncol*. 2015;46(1):414-422.
9. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(2):122-137.
10. Strong MS, Jako GJ. Laser surgery in the larynx. Early clinical experience with continuous CO_2 laser. *Ann Otol Rhinol Laryngol*. 1972;81(6):791-798.
11. Steiner W. Experience in endoscopic laser surgery of malignant tumours of the upper aero-digestive tract. *Adv Otorhinolaryngol*. 1988;39:135-144.
12. Steiner W, Ambrosch P, Hess CF, Kron M. Organ preservation by transoral laser microsurgery in piriform sinus carcinoma. *Otolaryngol Head Neck Surg*. 2001;124(1):58-67.
13. Canis M, Ihler F, Wolff HA, Christiansen H, Matthias C, Steiner W. Oncologic and functional results after transoral laser microsurgery of tongue base carcinoma. *Eur Arch Otorhinolaryngol*. 2013;270(3):1075-1083.
14. Canis M, Martin A, Ihler F, et al. Transoral laser microsurgery in treatment of pT2 and pT3 glottic laryngeal squamous cell carcinoma—results of 391 patients. *Head Neck*. 2014;36(6):859-866.
15. Canis M, Ihler F, Martin A, Matthias C, Steiner W. Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. *Head Neck*. 2014;37(6):889-895.
16. Canis M, Ihler F, Martin A, Wolff HA, Matthias C, Steiner W. Organ preservation in T4a laryngeal cancer: is transoral laser microsurgery an option? *Eur Arch Otorhinolaryngol*. 2013;270(10):2719-2727.
17. Sobin LH, Compton CC. TNM seventh edition: what's new, what's changed: communication from the International Union Against Cancer and the American Joint Committee on Cancer. *Cancer*. 2010;116(22):5336-5339.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471-1474.
19. Weiss BG, Ihler F, Wolff HA, et al. Transoral laser microsurgery for treatment for hypopharyngeal cancer in 211 patients. *Head Neck*. 2017;39(8):1631-1638.
20. Steiner W, Ambrosch P. *Endoscopic Laser Surgery of the Upper Aerodigestive Tract with Special Emphasis on Cancer Surgery*. Stuttgart, Germany: Thieme; 2000:147.
21. David SWH, Bruce H, Manuel B-S. *Transoral Laser Microsurgery for Cancer of the Upper Aerodigestive Tract*. Tuttlingen, Germany: Endo-Press; 2013.
22. Jackel MC, Ambrosch P, Martin A, Steiner W. Impact of re-resection for inadequate margins on the prognosis of upper aerodigestive tract cancer treated by laser microsurgery. *Laryngoscope*. 2007;117(2):350-356.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1954;58:457-481.
24. Grant DG, Hinni ML, Salassa JR, Perry WC, Hayden RE, Casler JD. Oropharyngeal cancer: a case for single modality treatment with transoral laser microsurgery. *Arch Otolaryngol Head Neck Surg*. 2009;135(12):1225-1230.
25. Rich JT, Milov S, Lewis JS Jr, Thorstad WL, Adkins DR, Haughey BH. Transoral laser microsurgery (TLM) +/− adjuvant therapy for advanced stage oropharyngeal cancer: outcomes and prognostic factors. *Laryngoscope*. 2009;119(9):1709-1719.
26. Haughey BH, Hinni ML, Salassa JR, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. *Head Neck*. 2011;33(12):1683-1694.
27. Karatzanis AD, Psychogios G, Waldfahrer F, Zenk J, Velegrakis GA, Iro H. Surgical management of T1 oropharyngeal carcinoma. *Head Neck*. 2012;34(9):1277-1282.
28. Iro H, Mantsopoulos K, Zenk J, Waldfahrer F, Psychogios G. Results of transoral laser resection in T1-2 oropharyngeal, hypopharyngeal and laryngeal carcinomas. *Laryngorhinootologie*. 2011;90(8):481-485.
29. Rogers SN, Pinto RS, Lancaster J, et al. Health related quality of life following the treatment of oropharyngeal cancer by transoral laser. *Eur Arch Otorhinolaryngol*. 2016;273(11):3913-3920.
30. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363(1):24-35.

31. Rahmati R, Dogan S, Pyke O, et al. Squamous cell carcinoma of the tonsil managed by conventional surgery and postoperative radiation. *Head Neck*. 2015;37(6):800-807.
32. Park YM, Kim HR, Cho BC, Keum KC, Cho NH, Kim SH. Transoral robotic surgery-based therapy in patients with stage III-IV oropharyngeal squamous cell carcinoma. *Oral Oncol*. 2017;75:16-21.
33. Moore EJ, Van Abel KM, Price DL, et al. Transoral robotic surgery for oropharyngeal carcinoma: surgical margins and oncologic outcomes. *Head Neck*. 2018;40(4):747-755.
34. Sinha P, Pipkorn P, Zenga J, Haughey BH. The hybrid transoral-pharyngotomy approach to oropharyngeal carcinoma: technique and outcome. *Ann Otol Rhinol Laryngol*. 2017;126(5):357-364.
35. Moore EJ, Olsen SM, Laborde RR, et al. Long-term functional and oncologic results of transoral robotic surgery for oropharyngeal squamous cell carcinoma. *Mayo Clin Proc*. 2012;87(3):219-225.
36. Moncrieff M, Sandilla J, Clark J, et al. Outcomes of primary surgical treatment of T1 and T2 carcinomas of the oropharynx. *Laryngoscope*. 2009;119(2):307-311.
37. Laccourreye O, Hans S, Menard M, Garcia D, Brasnu D, Holsinger FC. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. *Arch Otolaryngol Head Neck Surg*. 2005;131(7):592-599.
38. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*. 2004;22(1):69-76.
39. Mendenhall WM, Morris CG, Amdur RJ, et al. Definitive radiotherapy for tonsillar squamous cell carcinoma. *Am J Clin Oncol*. 2006;29(3):290-297.
40. Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Werning JW, Villaret DB. Definitive radiotherapy for squamous cell carcinoma of the base of tongue. *Am J Clin Oncol*. 2006;29(1):32-39.
41. Culie D, Garrel R, Viotti J, et al. Impact of HPV-associated p16-expression and other clinical factors on therapeutic decision-making in patients with oropharyngeal cancer: a GETTEC multicentric study. *Eur J Surg Oncol*. 2018;44:1908-1913.
42. Bernal-Sprekelsen M, Dazert S, Sudhoff H, Blanch JL, Vilaseca I. Complications of transoral laser surgery for malignant tumors of the larynx and hypopharynx. *Laryngorhinootologie*. 2009;88(1):28-34.
43. Alves HR, Ishida LC, Ishida LH, et al. A clinical experience of the supraclavicular flap used to reconstruct head and neck defects in late-stage cancer patients. *J Plast Reconstr Aesthet Surg*. 2012;65(10):1350-1356.
44. Welkoborsky HJ, Deichmuller C, Bauer L, Hinni ML. Reconstruction of large pharyngeal defects with microvascular free flaps and myocutaneous pedicled flaps. *Curr Opin Otolaryngol Head Neck Surg*. 2013;21(4):318-327.
45. Welz C, Canis M, Schwenk-Zieger S, Spiegel JL, Weiss BG, Pilavakis Y. Oral cancer reconstruction using the supraclavicular artery island flap: comparison to free radial forearm flap. *J Oral Maxillofac Surg*. 2017;75(10):2261-2269.
46. Late effects consensus conference: RTOG/EORTC. *Radiother Oncol*. 1995;35(1):5-7.
47. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19):1945-1952.
48. Bernier J, Cooper JS. Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? *Oncologist*. 2005;10(3):215-224.
49. Yao M, Nguyen T, Buatti JM, et al. Changing failure patterns in oropharyngeal squamous cell carcinoma treated with intensity modulated radiotherapy and implications for future research. *Am J Clin Oncol*. 2006;29(6):606-612.
50. Setton J, Lee NY, Riaz N, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. *Cancer*. 2015;121(2):294-301.

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Transoral laser microsurgery or total laryngectomy for recurrent squamous cell carcinoma of the larynx: Retrospective analysis of 199 cases

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ABSTRACT: *Background.* Surgical treatment options for local recurrences of laryngeal cancer can be either organ-preserving surgery or total laryngectomy. The purpose of this study was to present our evaluation of the treatment with transoral laser microsurgery (TLM) in comparison to laryngectomy.

Methods. We conducted a retrospective review of 199 consecutive patients with recurrent laryngeal cancer at 1 tertiary referral center.

Results. The 5-year overall survival, disease-specific survival, and local control rates were 64.8%, 79.6%, and 57.5%, respectively, for 93 patients with early tumors treated by TLM, 28.9%, 41.7%, and 43.7%, respectively, for 52 patients with advanced tumors treated by TLM as well as 39.4%, 44.6%, and 68.8%, respectively, for 54 patients with advanced tumors treated by total laryngectomy. Five-year larynx-preservation rate was 77.7% for early as well as 68.4% for advanced tumors treated by TLM.

Conclusion. TLM is an option in early and in selected cases of advanced locally recurrent laryngeal cancer. © 2017 Wiley Periodicals, Inc. *Head Neck* **39:** 1166–1176, 2017

KEY WORDS: laryngeal neoplasms, neoplasm recurrence, local, laryngectomy, transoral laser microsurgery, retrospective study

INTRODUCTION

Transoral laser microsurgery (TLM) is a long-established first-line treatment option for laryngeal squamous cell carcinoma.[1,2] For early-stage tumors, radiotherapy is frequently preferred in North America,[3] whereas most European centers see more favorable outcomes using TLM[3–8] as single-modality treatment. For advanced tumors, beyond the oncologic outcome, larynx preservation is a main concern in treatment planning.[9] Convincing results also support the use of TLM for organ-preserving surgery in advanced tumors with low morbidity, good functional results, and reliable oncologic outcome.[8,10,11] Traditionally pursued open partial laryngectomies are becoming less relevant.[9,12–16] Current guidelines support postoperative radiation with concomitant chemotherapy after surgical resection of advanced tumors.[15,17,18] However, very limited evidence exists from randomized controlled clinical trials.[4]

In recurrent laryngeal cancer, even less unambiguous recommendations exist.[19–25] The frequency of recurrences after successful first-line treatment of laryngeal cancer is given as up to 50% of patients.[21,26] Availability and morbidity of options in the recurrent situation depends on modalities already exploited for first-line treatment.[27]

Because surgery is not possible in every case,[27] primary irradiation is the treatment of choice in radiation-naïve unresectable recurrent tumors. In case irradiation already took place in an earlier sequence of therapy, reirradiation is afflicted with high toxicity and is discussed controversially.[22] Therefore, in unresectable radiorecurrent cases, cure is no longer possible. To slow tumor progression, platin-based chemotherapy with the addition of 5-fluorouracil and cetuximab is the standard of care in patients with a good performance status.[28]

For curative treatment of recurrent laryngeal cancer, surgery is the preferred modality for salvage.[22,25] Salvage surgery is technically challenging and multiple factors are to be considered, including initial and recurrent tumor stage, previous treatment, performance status, and tumor-free interval.[21,27] Notwithstanding its enormous functional disadvantages, total laryngectomy is an oncologically safe approach in recurrent laryngeal cancer because, in a great share of cases, a recurrence is confined to the larynx and can, therefore, be treated by ablative surgery.[21] Technical feasibility and more predictable outcomes might be an aspect in recommendations for total laryngectomy in recurrent laryngeal cancer.[19,24,29,30]

Organ preservation, however, is also desirable in the salvage situation. TLM is possible after previous irradiation[24,25] and additionally provides the benefits of a transoral approach, thereby making treatment complication, such as chondronecrosis or fistula, unlikely.[19] It can be tailored to the extent of the

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recurrent tumor without reconstructive limitations[19] and can be repeated for persistent or recurrent disease.[31] Functional outcomes after organ-preserving salvage surgery by TLM are reported to be favorable,[32] and tracheostomy as well as nasogastric feeding tubes are not routinely required.[31] By application of frozen sections, even difficult recurrence patterns, like submucosal tumor growth and multifocal development, can be successfully managed by TLM.[23,31] This makes it desirable to delineate the applicability of TLM according to the extent of tumor recurrence and compare the oncologic outcome to total laryngectomy, because the latter constitutes the oncologic benchmark for all procedures that promise less functional constraints.

Therefore, the purpose of this study was to present our evaluation of the results of patients with recurrent laryngeal cancer treated at 1 tertiary referral center to address the following questions: (1) is transoral laser microsurgery an option in recurrent laryngeal squamous cell carcinoma and (2) how are the results of TLM for early and advanced recurrent laryngeal tumors compared to total laryngectomy for advanced cases?

PATIENTS AND METHODS

Ethics and study center

The institutional review board (Ethikkommission der Universitätsmedizin Göttingen, Göttingen, Germany), approved this retrospective chart review with the reference number 13/7/16. The study is in accordance with the ethical standards of the Helsinki Declaration of 1975 in the form of the current seventh revision (2013). Patients' data were kept anonymously after extraction from the original medical records. Data were analyzed from all patients treated consecutively at 1 tertiary referral center, the Department of Otorhinolaryngology, University Medical Center Göttingen, Göttingen, Germany.

Study design, inclusion, and exclusion of patients

We reviewed the available medical records of all patients with squamous cell carcinoma of the supraglottic or glottic larynx who consecutively underwent TLM with curative intent at the study center between 1986 and 2014. Cases were drawn from a prospective database that included all patients with head and neck squamous cell carcinoma. Earlier results from that database regarding recurrences of laryngeal tumors have been published before.[33–35]

Statistical analyses were carried out stratified for treatment groups. Data assessments were similar in all treatment groups. Because of the retrospective nature of the analysis, several types of bias could not be avoided. However, by including all consecutively treated patients into this analysis, selection and reporting bias should be limited to a minimum.

For the present analyses, we included patients (1) with squamous cell carcinoma of the larynx and (2) local or locoregional recurrence that were (3) treated with either TLM or total laryngectomy. Exclusion criteria were: (1) regional recurrences without local recurrence; (2) tumors with an origin outside of the larynx; (3) distant metastases; (4) patients treated with open surgery; and (5) inoperable tumors.

Follow-up und identification of tumor recurrence

After completion of treatment for initial tumor occurrence, patients were seen at the Department of Otorhinolaryngology every 3 months for 3 years and every 6 months for the following 2 years. After that, appointments were made once a year. Unscheduled visits at the department could be made anytime in case of new symptoms, including but not limited to pain, dysphagia, or dyspnea.

Diagnostic approach included anamnesis focused on pain, speech, and swallowing. Clinical examinations on awake patients at each visit consisted of direct and indirect inspection of the upper aerodigestive tract, including magnifying laryngoscopy and palpation of the neck. At least at every second visit, an ultrasonography of the neck was performed.

CT scan of the neck and thorax as well as ultrasonography of the abdomen was performed in recurrent supraglottic cancer or recurrent glottic cancer of Union for International Cancer Control (UICC) stage II or higher. In patients with UICC stage I glottic cancer recurrence, staging was confined to ultrasonography of the neck. Panendoscopy included rigid tracheobronchoscopy and esophagoscopy, direct pharyngoscopy, and microlaryngoscopy, and was performed in all patients for histopathological confirmation of recurrence and to diagnose any second primary tumor of the upper aerodigestive tract.

TLM was performed using a CO_2 laser (C40, later AcuPulse 40; Lumenis Germany GmbH, Dreieich, Germany) in the continuous superpulse mode. The step-by-step technique for tumor resection initially described by Steiner[1] involved cutting through the tumor under microscopic magnification. This enables differentiation between tumor and healthy tissue and allows the surgeon to follow tumor growth while preserving as much healthy tissue as possible. Total laryngectomy included laryngopharyngectomy with reconstruction by microvascular or pedicled flaps when necessary.

Elective neck dissection in rcN0 recurrent supraglottic tumors was carried out to include levels II and III bilaterally, in case it had not been performed before. In rcN0 cases of recurrent glottic tumors, neck dissection was not routinely performed. In case of clinically suspected or manifest regional spread, neck dissection or neck dissection revision always included the affected levels.

Radiotherapy and chemotherapy

Treatment decisions, including the addition of radiation and chemotherapy, were made interdisciplinary by consent of specialists for otorhinolaryngology, radiation oncology, and medical oncology. Although surgical treatment took place at 1 tertiary referral center, radiotherapy or chemoradiotherapy was administered over 6 weeks 5 times a week in an outpatient setting at the facility nearest to the patient's residence. Patients were treated in at least 6 different facilities with varying protocols. Generally, most centers, until 2001, treated patients with radiotherapy alone or with the addition of carboplatin. Since 2002, at more and more centers, concomitant cisplatin was applied. Chemotherapy was not added in case of patient refusal, reduced general condition, or inadequate renal function.

Outcome measures and statistical analyses

Data is reported as mean ± SD or median values throughout this work. Survival data was calculated by the

TABLE 1. Demographic and clinical data of 199 patients with recurrent laryngeal cancer by treatment group.

Variables	All patients	Treatment group		
		TLM early	TLM advanced	Total laryngectomy
Age, y				
Mean ± SD	63.0 ± 11.6	65.7 ± 12.0	61.4 ± 11.4	64.2 ± 11.9
Range	33.4–90.9	35.2–90.9	40.6–85.2	33.4–76.2
Sex, no. of patients				
Male	176	81	45	50
Female	23	12	7	4
Localization, no. of patients				
Supraglottis	37	14	9	14
Glottis	162	79	43	40
Mode of recurrence, no. of patients				
Local only	175	93	43	39
Local + regional	24	0	9	15
Total no. of patients	199	93	52	54

Abbreviation: TLM, transoral laser microsurgery.

Kaplan–Meier product limit estimator by Dell Statistica version 12 (Dell, Round Rock, TX). Statistical differences between groups were calculated by the log-rank test. A value of $p < .05$ was considered to be statistically significant. In the present analysis, missing data were encountered only in the form of patients lost to follow-up.

In the Kaplan–Meier calculations, lost to follow-up or alive without evidence of tumor was always considered as censored observation. For overall survival, death regardless of cause was counted as an event. For the disease-specific survival rate, death related to the tumor was counted as an event, whereas death from other causes was counted as censored. For the laryngectomy-free survival rate, laryngectomy or death regardless of the cause was counted as an event.

For the local control rate, only local recurrence of cancer was counted as an event. For the larynx-preservation rate, only laryngectomy was counted as an event. For the local recurrence-free larynx-preservation rate, laryngectomy or local recurrence of cancer was counted as an event. Death regardless of the cause was considered a censored observation for the local control rate, the larynx-preservation rate, and the local recurrence-free larynx-preservation rate.

Statistical analyses were carried out stratified for treatment groups. Patients with T1 or T2 tumors and treatment by TLM constituted the "TLM early" treatment group and patients with T3 or T4 tumors and treatment by TLM constituted the "TLM advanced" treatment group. Total laryngectomy was only performed in patients with T3 or T4 tumors. Those strata were chosen to improve comparability between advanced tumors treated by TLM or total laryngectomy.

This report was prepared according to the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement, as far as it was applicable to the present study.[36] The corresponding checklist is given in Supplementary Table S1, online only.

RESULTS

Eligible patients and characteristics of study population

A total of 1002 patients were treated with TLM for primary squamous cell carcinoma of the larynx at the study center in the timespan investigated. After the initial treatment, those patients were followed for an average time of 76.7 ± 53.4 months. Two hundred fifty-seven of the 1002 patients (25.6%) developed a recurrence after an average of 24.7 ± 25.9 months. The mean age at the time of diagnosis of the recurrence was 63.1 ± 11.8 years. Not all patients were eligible for inclusion into the present study.

Fifty-eight of the 257 patients with recurrent laryngeal cancer were excluded from further analyses. Twenty-seven patients (10.5%) thereof had regional recurrence only and were treated by surgery alone in 9 cases and by surgery and postoperative radiotherapy in 18 cases. Twenty-eight patients' (10.9%) were deemed to be inoperable and received primary radiation in 8 cases or best supportive care in 20 cases. Three patients (1.2%) were treated surgically with open partial laryngectomy. This treatment approach was reserved for special cases only at the study center during the timespan investigated and was, therefore, not included in the further analyses.

Tumor categories and tumor stage

One hundred ninety-nine of the 257 patients with recurrent laryngeal cancer were eligible for analysis in the present study and received either TLM or total laryngectomy for salvage treatment. Demographic and clinical data of those patients are given in Table 1. The T classification and N classification for the initial occurrence of laryngeal cancer is given in Table 2. Taken together, 7 patients had UICC stage 0, 62 had stage I, 62 had stage II, 44 had stage III, and 24 had stage IVa disease at the initial occurrence of the tumor. A total of 10 patients had received postoperative radiotherapy for the treatment of the initial occurrence of tumor. The T classification and N classification for the recurrence of laryngeal cancer is given in Table 3. At the time of recurrence, 7 patients had UICC stage 0, 53 had stage I, 33 had stage II, 24 had stage III, 81 had stage IVa, and 1 had stage IVb disease.

Of the 199 patients, salvage TLM was performed in 145 patients (72.9%), whereas total laryngectomy was the treatment of choice in 54 patients (27.1%). For the sake of comparability, the 145 patients with salvage TLM are considered in 2 separate strata in the following analyses,

TABLE 2. pT classification versus cN/pN classification of 199 patients with recurrent laryngeal cancer at the time of initial tumor occurrence.

	cN0	pN0	pN1	pN2a	pN2b	pN2c	pN3	Total
pTis	7	0	0	0	0	0	0	7
pT1*	1	0	0	0	0	0	0	1
pT1a†	48	1	0	0	0	0	0	49
pT1b†	11	1	0	0	0	0	0	12
pT2	48	14	3	0	0	0	0	65
pT3	18	18 (2)	5 (1)	0	4 (2)	0	0	45 (5)
pT4a	5 (2)	6	3	0	4 (1)	2 (2)	0	20 (5)
Total	138 (2)	40 (2)	11 (1)	0	8 (3)	2 (2)	0	199 (10)

Abbreviation: cN0, clinically no suspect lymph nodes and, therefore, no neck dissection performed.
* pT1 in supraglottic tumors only.
† pT1a/pT1b in glottic tumors only.
In brackets are the number of patients who were treated with adjuvant radiotherapy for initial occurrence of tumor.

the TLM early treatment group (93 patients) and the TLM advanced treatment group (52 patients). The TLM early treatment group consisted of 7 patients with rpTis, 49 with rpT1a, 4 with rpT1b, and 33 with rpT2 category of recurrent primary tumor. The TLM advanced treatment group consisted of 19 patients with rpT3 and 33 with rpT4a. The group treated with total laryngectomy exhibited rpT3 in 7 cases and rpT4a category in 47 cases.

Neck dissection because of clinically manifest or suspected regional spread of the recurrent tumor was performed in the TLM early treatment group in 6 patients (6.5%; 2 thereof revisions), in the TLM advanced treatment group in 9 patients (17.3%; 3 revisions), and in the group treated with total laryngectomy in 30 patients (55.6%; 10 revisions).

In the TLM early treatment group, 2 patients (2.2%) had received postoperative radiotherapy for the treatment of the initial occurrence of laryngeal cancer and were, therefore, radiorecurrent with surgery as the only option. This was also the case in 1 patient (1.9%) in the TLM advanced treatment group and 7 patients in the group treated with total laryngectomy (13.0%). All other patients of the respective groups were potentially eligible for postoperative radiotherapy after the surgical treatment of recurrence. These were 91 in the TLM early treatment group, 51 in the TLM advanced treatment group, and 47 in the group treated with total laryngectomy. In the TLM early treatment group, 1 patient (1.1% of eligible) received postoperative radiotherapy after the surgical treatment of the recurrence. This was also the case in the TLM advanced treatment group in 17 patients (33.3%) and in the group treated with total laryngectomy in 21 patients (44.7%). After surgical treatment of recurrent laryngeal cancer either by TLM or by total laryngectomy, patients were seen in a structured follow-up program for an average of 45.5 ± 45.2 months.

Survival

After surgical treatment of recurrent laryngeal cancer by TLM or laryngectomy, the 5-year overall survival rate was 64.8%, 28.9%, and 39.4% in the TLM early treatment group, the TLM advanced treatment group, and the group treated with total laryngectomy, respectively. Median overall survival was 49.2 months, 25.7 months, and 25.9 months, respectively. There was a statistically significant difference in the overall survival rate between the TLM early treatment group and the TLM advanced treatment group as well as the TLM early treatment group and the group treated with total laryngectomy ($p < .001$, Kaplan–Meier log-rank test), whereas there was no statistically significant difference in survival between the TLM advanced treatment group and the group treated with total laryngectomy (Figure 1A, Table 4).

The 5-year disease-specific survival rate was 79.6%, 41.7%, and 44.6% in the TLM early treatment group, the TLM advanced treatment group, and the group treated with total laryngectomy, respectively. Median disease-specific survival was 49.2 months, 25.7 months, and 25.9 months, respectively. There was again a statistically significant difference in

TABLE 3. rpT versus rcN/rpN classification of 199 patients with recurrent laryngeal cancer at the time of recurrence.

	rcN0	rpN0	rpN1	rpN2a	rpN2b	rpN2c	rpN3	Total
rpTis	7	0	0	0	0	0	0	7
rpT1*	7 (2)	1	0	0	0	0	0	8 (2)
rpT1a†	39	2	0	0	0	0	0	41
rpT1b†	4	0	0	0	0	0	0	4
rpT2	30	3	0	0	0	0	0	33
rpT3	13 (1)	7	4	0	2	0	0	26 (1)
rpT4a	28 (1)	34 (6)	6	0	5	6	1	80 (7)
Total	128 (4)	47 (6)	10	0	7	6	1	199 (10)

Abbreviation: rcN0, clinically no suspect lymph nodes and no neck dissection performed.
* rpT1 in supraglottic tumors only.
† rpT1a/rpT1b in glottic tumors only.
In brackets are the number of patients who were treated with adjuvant radiotherapy for initial occurrence of tumor.

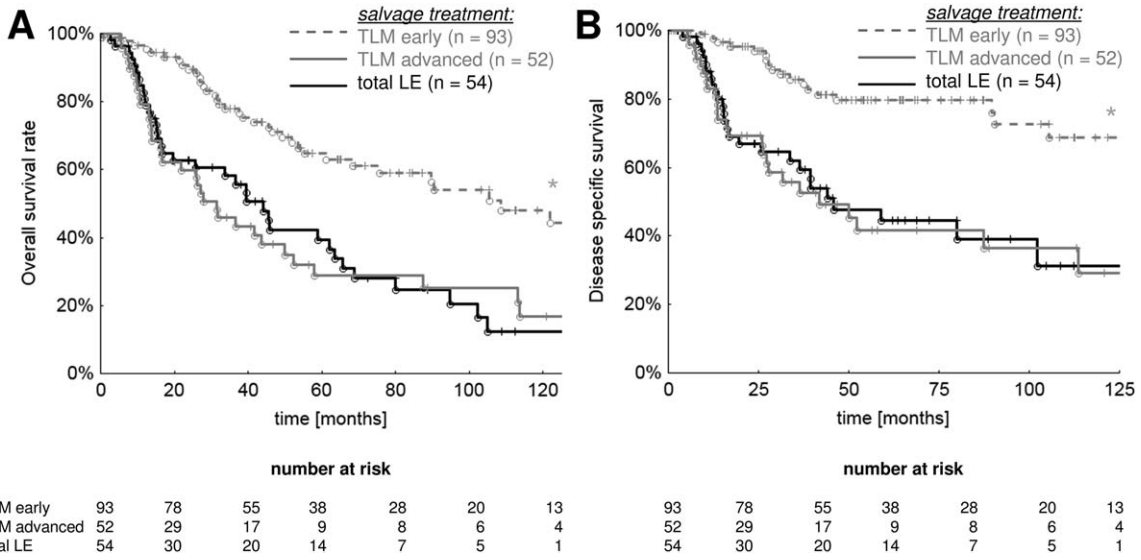

FIGURE 1. Survival of 199 patients treated either with transoral laser microsurgery (TLM) for early or advanced recurrent laryngeal squamous cell carcinoma or with total laryngectomy (LE). (A) Overall survival, *$p < .001$ TLM early treatment group versus TLM advanced treatment group and TLM early treatment group versus the group treated with total laryngectomy. (B) Disease-specific survival, *$p < .001$ TLM early treatment group versus TLM advanced treatment group and TLM early treatment group versus the group treated with total laryngectomy. Kaplan–Meier survival estimator; gray plots = TLM; black plot = total laryngectomy; circles = event; and cross = censored observation.

disease-specific survival rate between the TLM early treatment group and the TLM advanced treatment group, as well as in the TLM early treatment group and the group treated with total laryngectomy ($p < .001$, Kaplan–Meier log-rank test), although there was no statistically significant difference in survival between the TLM advanced treatment group and the group treated with total laryngectomy (Figure 1B, Table 4).

At the time of last follow-up, 55 patients were alive in the TLM early treatment group, 18 in the TLM advanced treatment group, and 17 in the group treated with total laryngectomy. Thirty-eight patients died during the observation period in the TLM early treatment group, 34 in the TLM advanced treatment group, and 37 in the group treated with total laryngectomy.

Second recurrences

Ninety-two of 199 patients (46.2%) treated with either TLM or total laryngectomy for recurrent laryngeal cancer showed a second recurrence. The median time from treatment of the first recurrence to a second recurrence was 8.8 months. In 58 of 92 cases (63.0%), the second recurrence developed locally only. In 15 cases (16.3%), the second recurrence was local and regional, in a further 15 cases (16.3%) it was regional only, and in 4 cases (4.3%) it was with distant metastases.

In the TLM early treatment group, the TLM advanced treatment group, and the group treated with total laryngectomy, the local control rate after 5 years was 57.5%, 43.7%, and 68.8%, respectively. In this study, the group treated with total laryngectomy showed the best result with the difference of the local control rate being statistically significant between the group treated with total laryngectomy and the TLM advanced treatment group ($p < .05$, Kaplan–Meier log-rank test). There was no significant difference between the other groups. Figure 2 provides an overview of the local control rate by treatment group. A comprehensive overview of local control rates by month is given in Table 4.

Forty-four of 93 patients (47.3%) developed a second recurrence in the TLM early treatment group, 30 of 52 patients (57.7%) in the TLM advanced treatment group, and 18 of 54 patients (33.3%) in the group treated with total laryngectomy. Seventy-nine of 151 patients (52.3%) without postoperative radiotherapy developed a second recurrence, whereas 13 of 48 patients (27.1%) after postoperative radiotherapy did so.

Salvage treatment for the 92 patients with second recurrences of laryngeal cancer was TLM only in 28 cases, TLM and postoperative radiotherapy in 9, laryngectomy alone in 10, laryngectomy and postoperative radiotherapy in 10, neck dissection only in 5 (2 thereof revisions), neck dissection and postoperative radiotherapy in 7 (3 thereof neck dissection revisions), open partial laryngectomy alone in 1, open partial laryngectomy in 1, and postoperative radiotherapy in 1, as well as radiotherapy alone in 8 cases. Thirteen patients received palliative care after the second recurrence of laryngeal cancer.

Functional results

By using TLM for the treatment of recurrent laryngeal cancer, it was possible to preserve the larynx even in advanced recurrent tumors in a considerable share of patients. In the TLM early treatment group, 19 of 93 patients (20.4%) eventually lost the larynx despite initially successful salvage TLM after a median of 15.6 months. In 18 patients, this was due to one or more further recurrences, and in 1 patient because of functional reasons. In the TLM advanced treatment group, 12 of 52 patients (23.1%) required a laryngectomy be performed after initially successful salvage TLM after a median duration of 7.1 months. In 11 patients, this was due to one or more further

TABLE 4. Comprehensive overview of survival, local control, and larynx-preservation rates of 199 patients with recurrent laryngeal cancer by treatment group.

Parameter	Treatment group	Outcome, timepoint in months							*p* value
		12	24	36	48	60	120	180	
Overall survival rate	TLM early ($n = 93$)	96.7%	89.6%	78.0%	71.0%	64.8%	48.0%	24.4%	TLM early vs TLM advanced: $p < .001$*
	TLM advanced ($n = 52$)	79.4%	60.0%	45.9%	37.9%	28.9%	16.9%	16.9%	TLM early vs total laryngectomy: $p < .001$*
	Total laryngectomy ($n = 54$)	80.9%	62.9%	58.2%	42.3%	39.4%	12.3%	0.0%	TLM advanced vs total laryngectomy: $p = .975$
Disease-specific survival rate	TLM early ($n = 93$)	98.9%	94.1%	85.8%	79.6%	79.6%	68.7%	62.9%	TLM early vs TLM advanced: $p < .001$*
	TLM advanced ($n = 52$)	83.1%	69.2%	55.6%	49.2%	41.7%	29.2%	29.2%	TLM early vs total laryngectomy: $p < .001$*
	Total laryngectomy ($n = 54$)	86.1%	66.9%	61.9%	47.8%	44.6%	31.2%	31.2%	TLM advanced vs total laryngectomy: $p = .820$
Local control rate	TLM early ($n = 93$)	74.0%	64.3%	59.6%	59.6%	57.5%	46.4%	38.6%	TLM early vs TLM advanced: $p = .159$
	TLM advanced ($n = 52$)	66.6%	57.9%	43.7%	43.7%	43.7%	36.4%	36.4%	TLM early vs total laryngectomy: $p = .195$
	Total laryngectomy ($n = 54$)	83.9%	71.8%	68.8%	68.8%	68.8%	68.8%	68.8%	TLM advanced vs total laryngectomy: $p < .05$*
Larynx preservation rate	TLM early ($n = 93$)	89.8%	80.9%	79.4%	77.7%	77.7%	77.7%	69.9%	TLM early vs TLM advanced: $p = .276$
	TLM advanced ($n = 52$)	100.0%	68.4%	68.4%	68.4%	68.4%	68.4%	68.4%	
Local recurrence-free larynx preservation rate	TLM early ($n = 93$)	74.0%	64.3%	59.6%	58.0%	55.8%	45.0%	37.5%	TLM early vs TLM advanced: $p = .563$
	TLM advanced ($n = 52$)	62.4%	53.4%	38.5%	38.5%	38.5%	30.8%	30.8%	
Laryngectomy-free survival rate	TLM early ($n = 93$)	86.7%	73.5%	63.1%	57.6%	54.3%	41.8%	13.0%	TLM early vs TLM advanced: $p < .05$*
	TLM advanced ($n = 52$)	63.0%	47.7%	32.9%	27.4%	21.3%	17.1%	17.1%	

Abbreviation: TLM, transoral laser microsurgery.
The *p* values for differences were tested with the Kaplan–Meier log-rank test.
*These figures indicate statistical significance.

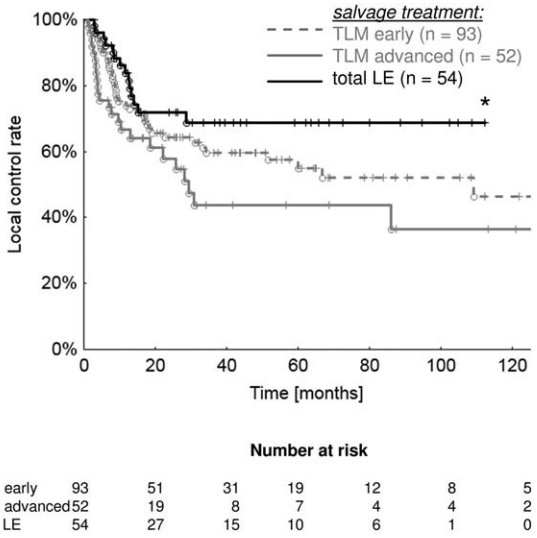

FIGURE 2. Local control of 199 patients treated either with transoral laser microsurgery (TLM) for early or advanced recurrent laryngeal squamous cell carcinoma or with total laryngectomy (LE). Kaplan–Meier survival estimator; gray plots = TLM; black plot = total laryngectomy; circles = event; and cross = censored observation. *$p < .05$ group treated with total laryngectomy versus TLM advanced treatment group.

recurrences, and in 1 patient because of functional reasons. The 5-year larynx-preservation rate was 77.7% in the TLM early treatment group and 68.4% in the TLM advanced treatment group. The larynx-preservation rate by treatment group is given in Figure 3 and Table 4.

From an oncologic perspective and from the patients point of view, combined outcome measures that also take into account local control or survival might be even more meaningful than larynx-preservation alone. A combined parameter of local control and larynx preservation is therefore termed local recurrence-free larynx-preservation rate. The 5-year result for the TLM early treatment group was 55.8%, whereas patients from the TLM advanced treatment group achieved 38.5% (Figure 4A, Table 4). The combined parameter of overall survival and larynx preservation is termed the laryngectomy-free survival rate. The 5-year result for the TLM early treatment group was 54.3%, whereas patients from the TLM advanced treatment group achieved 21.3% (Figure 4B, Table 4). The difference in laryngectomy-free survival between the groups was statistically significant ($p < .05$, Kaplan–Meier log-rank test).

In most patients treated with TLM, not only laryngectomy but also permanent or even temporary tracheotomy could be avoided. Patients in the TLM early treatment group had a tracheotomy in only 3 of 93 cases (3.2%), 2 of which were temporary. In the TLM advanced treatment group, 9 of 52 patients (17.3%) had a tracheotomy, 5 of which were temporary. Only singular cases were permanently dependent on a percutaneous endoscopic gastrostomy (PEG) tube for nutrition. When the localization of the primary tumor is considered, in general, glottic tumors had more favorable functional results than supraglottic tumors (Table 5).

Complications and revisions

After TLM for recurrent laryngeal cancer, synechia of the vocal fold was observed in 2 of 93 patients in the TLM early treatment group (2.2%) and 1 of 52 patients in the TLM advanced treatment group (1.9%). All cases could be resolved by repeated TLM procedures. Postoperative tracheostomies as emergency procedures because of swelling or bleeding had to be carried out in 1 of 93 patients in the TLM early treatment group (1.1%) and 2 of 52 patients in the TLM advanced treatment group (3.8%).

One of 52 patients (1.9%) in the TLM advanced treatment group developed an emphysema of the neck postoperatively that could be resolved conservatively by dressing and administration of antibiotic agents. One of 54 patients (1.9%) in the group treated with total laryngectomy developed a pharyngocutaneous fistula that resolved with dressing, administration of antibiotic agents, and suppression of salivation by triple anticholinergic agents (glycopyrronium bromide, scopolamine hydrobromide, and botulinum toxin). This patient had received postoperative radiotherapy after the first occurrence of laryngeal cancer. No deaths were registered perioperatively in any treatment group.

DISCUSSION

This retrospective study evaluated the results with repeated TLM for recurrent squamous cell carcinoma of the larynx. Profound differences were seen for TLM in early recurrences compared with advanced tumors. In survival rates, early tumors treated by TLM achieved the best results, whereas advanced tumors treated by TLM had comparable results to total laryngectomy. Laryngectomy was able to provide the highest rate of local control in mostly advanced tumors, whereas the survival rates were comparable between TLM and laryngectomy. In case of treatment with TLM, the larynx-preservation rates of early tumors exceeded the rates for advanced tumors.

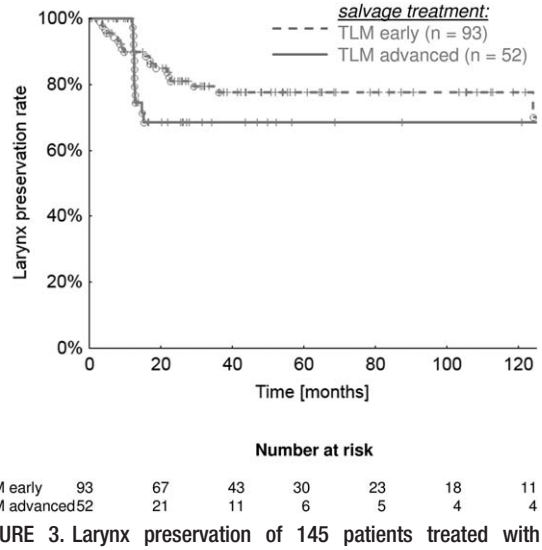

FIGURE 3. Larynx preservation of 145 patients treated with transoral laser microsurgery (TLM) for early or advanced recurrent laryngeal squamous cell carcinoma. Kaplan–Meier survival estimator; gray plots = TLM; circles = event; and cross = censored observation.

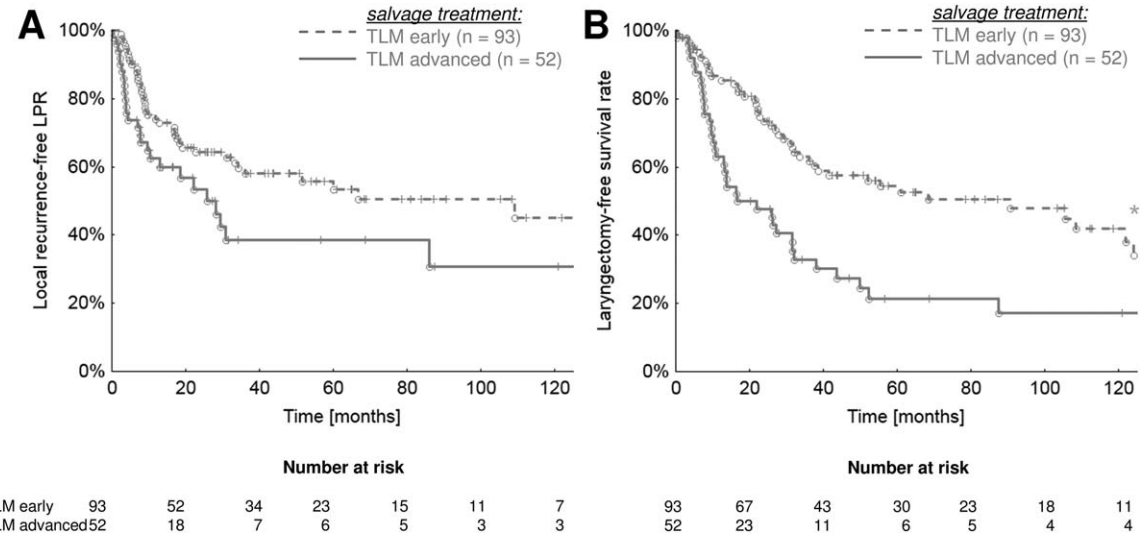

FIGURE 4. Combined local control, survival, and larynx preservation of 145 patients treated with transoral laser microsurgery (TLM) for early or advanced recurrent laryngeal squamous cell carcinoma. (A) Local recurrence-free larynx preservation rate (LPR). (B) Laryngectomy-free survival rate, *$p < .05$ TLM early treatment group versus TLM advanced treatment group. Kaplan–Meier survival estimator; gray plots = TLM; circles = event; and cross = censored observation.

As a limitation, a selection bias is to be taken into consideration when the present results of TLM and laryngectomy are compared. Most likely, a positive selection for tumor size and functional prognosis occurred for TLM, whereas a likewise negative selection is to be acknowledged for laryngectomy, as suggested by current recommendations.[21,25,27] This bias also applies to the reporting of results of recurrent laryngeal cancer in general, as noted before.[25] To improve transparency and comparability, the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement were followed for the presentation of this study.[36] Functional assessment was mainly based on larynx preservation and the continued use of PEG tubes or tracheostomy. Swallowing or breathing function could not be acknowledged directly, because available documentation was not sufficient. As suggested before,[37] this study analyzed a composite endpoint consisting of functional and oncologic aspects in the laryngectomy-free survival rate.

Further strengths of the present report include a high number of patients. Only 2 earlier studies analyzed more patients with recurrent laryngeal cancer so far.[27,38] Beyond that, an average follow-up time of 76.7 ± 53.4 months after initial tumor treatment and 45.5 ± 45.2 months after treatment of recurrence was only surpassed by 4 studies from the past decade.[31,34,35,39,40] The patients reported here constitute a highly homogenous collective treated by TLM initially with the results of repeated TLM or total laryngectomy contrasted for early and advanced tumors in separate groups. Recent investigations into the treatment of recurrent laryngeal cancer, however, have placed more focus on radiorecurrence[33,34,38,41–51] with less studies covering recurrences after initial surgery.[26,35,39,40,52,53]

In the present study, results after 2 years of follow-up were an overall survival rate in the TLM early treatment group, the TLM advanced treatment group, and the group treated with total laryngectomy of 89.6%, 60.0%, and 62.9%, a disease-specific survival rate of 94.1%, 69.2%, and 66.9%, a local control rate of 64.3%, 57.9%, and 71.8%, respectively, as well as a larynx-preservation rate of 80.9% for the TLM early treatment group and 68.4% for the TLM advanced treatment group. Two-year survival rates can be obtained from several meta-analyses from the literature. A systematic meta-analysis of TLM in radiorecurrent laryngeal cancer reporting pooled results from 11 studies, including 288 patients, found the 2-year rates of 74.8% for

TABLE 5. Functional results of 199 patients with recurrent laryngeal cancer.

	Temporary tracheostomy, no. of patients	Permanent tracheostomy, no. of patients	Permanent PEG-tube, no. of patients
By treatment group			
TLM early (total $n = 93$)	2	1	1
TLM advanced (total $n = 52$)	5	4	1
Total laryngectomy (total $n = 54$)	0	All patients	2
By location of primary tumor			
Supraglottis ($n = 37$)	4	2	4
Glottis ($n = 162$)	3	3	0

Abbreviations: PEG, percutaneous endoscopic gastrostomy; TLM, transoral laser microsurgery.

overall survival, 70.9% for disease-specific-survival, 56.9% for local control, and 72.3% for larynx preservation.[24] For open partial laryngectomy in recurrent laryngeal cancer, a systematic meta-analysis reporting pooled results from 26 studies, including 560 patients, stated the 2-year rates of overall survival as 83.1%, disease-specific survival as 91.0%, local control as 86.9%, and larynx preservation as 83.9%.[29] It is important to note that the majority of patients in both meta-analyses were T2 or smaller,[24,29] thereby placing an emphasis on early-stage tumors. This places the results of overall survival and disease-specific survival in the present study better than earlier studies for the TLM early treatment group and worse for the TLM advanced treatment group, as well as the group treated with total laryngectomy. The local control was found to be marginally and the larynx-preservation rate was considerably higher for partial laryngectomy[29] compared to TLM for radiorecurrences[24] and to the results reported here. Because of selective consideration of early-stage tumors in both reviews, the results given there are most likely comparable to the TLM early treatment group in the present study. Therefore, we see our study as better stratification in early and advanced recurrences than performed earlier.

Five-year survival rates for recurrent laryngeal cancer are only found in individual studies so far. The present report found a 5-year overall survival rate of 64.8% for early and 28.9% for advanced recurrent tumors treated with TLM and 39.4% for treatment with total laryngectomy. Five-year overall survival for patients treated with TLM initially as well as for recurrences of laryngeal cancer have been given before as 61.6% to 89.9% for early[35,40] and 21.3% to 25.8% for advanced recurrent tumors.[35,53] After primary treatment with radiotherapy and salvage treatment by TLM, the 5-year overall survival rates for early recurrences were reported to be 76.0 to 91.0%,[48–51] whereas populations that include advanced recurrences found 53.0%.[33,34] So far, no study reported results in a selected group of advanced radiorecurrent tumors, as noted before.[24] Open partial laryngectomy for recurrent laryngeal cancer resulted in 5-year overall survival rates of 48% to 76%,[26,54] whereas for total laryngectomy it was reported as 27% to 57%.[20,41,43,55] Summarized, overall survival rates in the current report are in line with previous results.

In the present study, the 5-year disease-specific survival rate was 79.6% for early and 41.7% for advanced recurrences treated with repeated TLM. The rate for patients treated with total laryngectomy was 44.6%. Earlier reports showed rates for disease-specific survival after TLM for recurrent laryngeal carcinoma of 90% to 100.0%[40,48,49,51,52] in early and 68.6% to 85.7%[34,35,47] in advanced recurrences. For open partial laryngectomy, 5-year disease-specific survival rates of 58.0% to 82.0% were reported,[26,27,39] whereas for total laryngectomy, 35% to 71.7% are given in the literature.[20,41,43,44,56] The rates for TLM found elsewhere at first seem to be higher than reported here. A disease-specific survival rate of 100% seems unrealistic and, therefore, those results may, in part, be explained by statistical issues arising from small patient numbers and potential inconsistencies with the judgment of disease-specific death.

In the present study, a 5-year result of the larynx-preservation rate for the TLM early treatment group was 77.7%, whereas patients from the TLM advanced treatment group achieved 68.4%. Other studies reported larynx-preservation rates by TLM in early recurrences of 54.3% to 100%[40,48,49,52] and with TLM in advanced cases of 38.8% to 63.6%.[34,35,53] Although our results are generally in line with previous reports, again, it is to be acknowledged that published results frequently include more early recurrent tumors than reported here. Alternative methods resulted in larynx-preservation rates of 70% to 100%[39,42] for open partial laryngectomy with small patient numbers and, again, mostly early-stage tumors.

Several current recommendations suggest total laryngectomy as the treatment of choice for radiorecurrent tumors.[25] This is often justified by technical feasibility and more predictable outcomes for total laryngectomy in recurrent laryngeal cancer.[19] However, we suggest that TLM should be the option of first choice in early-stage recurrences of laryngeal cancer. Moreover, it may also be a valid concept for advanced recurrences with similar results compared to total laryngectomy. There is, however, a share of patients for whom total laryngectomy will be the best option, depending on anatomic and physiological factors of the patient and on tumor properties.

A fistula rate after salvage laryngectomy of 1.9% reported here contrasts reports from the literature, in which 8.3% to 42% are given.[20,41,43,46,55,57,58] However, compared to the literature, the patients from the present study were mostly radiation-naïve, whereas most other reports on the fistula rate after salvage laryngectomy deal with radiorecurrent laryngeal cancer. For the prevention of pharyngocutaneous fistula, flap reconstruction during total laryngectomy can be considered for patients at high risk of fistula development.[58] Although, in cases of radiorecurrence, in which surgery is the only option,[24,25] a clear advantage of conservation salvage surgery by TLM after primary or postoperative radiotherapy is the absence of postoperative fistula and less need for reconstruction.[58]

A disadvantage of TLM could be a supposedly higher rate of local recurrences. Local control has been shown before to be higher with total laryngectomy than with conservation surgery.[59] However, the loss of function that accompanies total laryngectomy is a strong incentive to pursue conservation surgery. An important aspect is that there is no significant difference in overall and disease-specific survival between comparable patient groups treated by TLM or total laryngectomy in the present report. Therefore, we see TLM as an appropriate and efficient treatment option for recurrent laryngeal cancer in the hand of experienced surgeons and by rigorous indication considering aspects like tumor size, exposure, and functional prognosis.

The use of postoperative (chemo-)radiation is surprisingly low in the patient group reported here. Possibly survival and local control rates could have been even better with more widely adoption of postoperative radiation. In accordance with current guidelines,[17] postoperative (chemo-)radiation to salvage surgery should be given in radiation-naïve recurrent cases on a regular basis.

CONCLUSION

TLM is an option in recurrent laryngeal cancer with superior results in early recurrences and results comparable to total laryngectomy in selected advanced

recurrences. Stratification into early and advanced tumors in clinical studies aids the drawing of conclusions. Future investigations should evaluate functional outcome in a prospective manner, including combined outcome parameters of functional and oncologic results.

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REFERENCES

1. Steiner W. Experience in endoscopic laser surgery of malignant tumours of the upper aero-digestive tract. *Adv Otorhinolaryngol* 1988;39:135–144.
2. Steiner W. Results of curative laser microsurgery of laryngeal carcinomas. *Am J Otolaryngol* 1993;14:116–121.
3. Chen JJ, Stessin A, Christos P, Wernicke AG, Nori D, Parashar B. Differences in survival outcome between stage I and stage II glottic cancer: a SEER-based analysis. *Laryngoscope* 2015;125:2093–2098.
4. Warner L, Chudasama J, Kelly CG, et al. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. *Cochrane Database Syst Rev* 2014;12:CD002027.
5. Yoo J, Lacchetti C, Hammond JA, Gilbert RW; Head and Neck Cancer Disease Site Group. Role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer: a systematic review. *Head Neck* 2014;36:1807–1819.
6. Spielmann PM, Majumdar S, Morton RP. Quality of life and functional outcomes in the management of early glottic carcinoma: a systematic review of studies comparing radiotherapy and transoral laser microsurgery. *Clin Otolaryngol* 2010;35:373–382.
7. Canis M, Ihler F, Martin A, Matthias C, Steiner W. Transoral laser microsurgery for T1a glottic cancer: review of 404 cases. *Head Neck* 2015;37:889–895.
8. Canis M, Martin A, Ihler F, et al. Transoral laser microsurgery in treatment of pT2 and pT3 glottic laryngeal squamous cell carcinoma – results of 391 patients. *Head Neck* 2014;36:859–866.
9. Forastiere AA, Weber RS, Trotti A. Organ preservation for advanced larynx cancer: issues and outcomes. *J Clin Oncol* 2015;33:3262–3268.
10. Canis M, Ihler F, Martin A, Wolff HA, Matthias C, Steiner W. Results of 226 patients with T3 laryngeal carcinoma after treatment with transoral laser microsurgery. *Head Neck* 2014;36:652–659.
11. Canis M, Ihler F, Martin A, Wolff HA, Matthias C, Steiner W. Organ preservation in T4a laryngeal cancer: is transoral laser microsurgery an option? *Eur Arch Otorhinolaryngol* 2013;270:2719–2727.
12. Suárez C, Rodrigo JP, Silver CE, et al. Laser surgery for early to moderately advanced glottic, supraglottic, and hypopharyngeal cancers. *Head Neck* 2012;34:1028–1035.
13. Silver CE, Beitler JJ, Shaha AR, Rinaldo A, Ferlito A. Current trends in initial management of laryngeal cancer: the declining use of open surgery. *Eur Arch Otorhinolaryngol* 2009;266:1333–1352.
14. Ambrosch P. The role of laser microsurgery in the treatment of laryngeal cancer. *Curr Opin Otolaryngol Head Neck Surg* 2007;15:82–88.
15. American Society of Clinical Oncology, Pfister DG, Laurie SA, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol* 2006;24:3693–3704.
16. Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann Oncol* 2015;26:1941–1947.
17. Grégoire V, Lefebvre J-L, Licitra L, Felip E; on behalf of the EHNS–ESMO–ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):v184–v186.
18. Gorphe P, Matias M, Moya–Plana A, et al. Results and survival of locally advanced AJCC 7th edition T4a laryngeal squamous cell carcinoma treated with primary total laryngectomy and postoperative radiotherapy. *Ann Surg Oncol* 2016;23:2596–2601.
19. Marioni G, Marchese–Ragona R, Kleinsasser NH, et al. Partial laryngeal surgery in recurrent carcinoma. *Acta Otolaryngol* 2015;135:119–124.
20. Putten L, Bree R, Doornaert PA, et al. Salvage surgery in post-chemoradiation laryngeal and hypopharyngeal carcinoma: outcome and review. *Acta Otorhinolaryngol Ital* 2015;35:162–172.
21. Rodrigo JP, Kowalski LP, Silver CE, et al. When is reoperative surgery not indicated for recurrent head and neck squamous cell carcinoma? *Eur Arch Otorhinolaryngol* 2015;272:259–262.
22. Strojan P, Corry J, Eisbruch A, et al. Recurrent and second primary squamous cell carcinoma of the head and neck: when and how to reirradiate. *Head Neck* 2015;37:134–150.
23. Zhong A, Xu X, Fan H, Wang L, Niu Y. Transoral laser microsurgery for recurrent laryngeal carcinoma after primary treatment: a systematic review and meta-analysis. *J Cancer Res Ther* 2015;11 Suppl 2:C173–C178.
24. Ramakrishnan Y, Drinnan M, Kwong FN, et al. Oncologic outcomes of transoral laser microsurgery for radiorecurrent laryngeal carcinoma: a systematic review and meta-analysis of English-language literature. *Head Neck* 2014;36:280–285.
25. Agra IM, Ferlito A, Takes RP, et al. Diagnosis and treatment of recurrent laryngeal cancer following initial nonsurgical therapy. *Head Neck* 2012;34:727–735.
26. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *Laryngoscope* 2000;110(3 Pt 2 Suppl 93):1–18.
27. Gañán L, López M, García J, Esteller E, Quer M, León X. Management of recurrent head and neck cancer: variables related to salvage surgery. *Eur Arch Otorhinolaryngol* 2016;273:4417–4424.
28. Sacco AG, Cohen EE. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. *J Clin Oncol* 2015;33:3305–3313.
29. Paleri V, Thomas L, Basavaiah N, Drinnan M, Mehanna H, Jones T. Oncologic outcomes of open conservation laryngectomy for radiorecurrent laryngeal carcinoma: a systematic review and meta-analysis of English-language literature. *Cancer* 2011;117:2668–2676.
30. Marioni G, Marchese–Ragona R, Pastore A, Staffieri A. The role of supracricoid laryngectomy for glottic carcinoma recurrence after radiotherapy failure: a critical review. *Acta Otolaryngol* 2006;126:1245–1251.
31. Marioni G, Marchese–Ragona R, Lucioni M, Staffieri A. Organ-preservation surgery following failed radiotherapy for laryngeal cancer. Evaluation, patient selection, functional outcome and survival. *Curr Opin Otolaryngol Head Neck Surg* 2008;16:141–146.
32. Fink DS, Sibley H, Kunduk M, et al. Functional outcomes after salvage transoral laser microsurgery for laryngeal squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2016;155:606–611.
33. Steiner W, Vogt P, Ambrosch P, Kron M. Transoral carbon dioxide laser microsurgery for recurrent glottic carcinoma after radiotherapy. *Head Neck* 2004;26:477–484.
34. Roedel RM, Matthias C, Wolff HA, Schindler P, Aydin T, Christiansen H. Transoral laser microsurgery for recurrence after primary radiotherapy of early glottic cancer. *Auris Nasus Larynx* 2010;37:474–481.
35. Roedel RM, Matthias C, Wolff HA, Christiansen H. Repeated transoral laser microsurgery for early and advanced recurrence of early glottic cancer after primary laser resection. *Auris Nasus Larynx* 2010;37:340–346.
36. 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;370:1453–1457.
37. Lefebvre JL, Ang KK; Larynx Preservation Consensus Panel. Larynx preservation clinical trial design: key issues and recommendations – a consensus panel summary. *Int J Radiat Oncol Biol Phys* 2009;73:1293–1303.
38. Li P, Hu W, Zhu Y, Liu J. Treatment and predictive factors in patients with recurrent laryngeal carcinoma: a retrospective study. *Oncol Lett* 2015;10:3145–3152.
39. Lucioni M, Bertolin A, Lionello M, Giacomelli L, Rizzotto G, Marioni G. Open partial horizontal laryngectomy for salvage after failure of CO_2 laser-assisted surgery for glottic carcinoma. *Eur Arch Otorhinolaryngol* 2016;273:169–175.
40. Huang J, Yu Z, Fang J, Chen X, Chen X, Huang Z. Salvage transoral laser microsurgery for early recurrent glottic carcinoma after primary laser treatment. *Acta Otolaryngol* 2013;133:531–537.
41. Sandulache VC, Vandelaar LJ, Skinner HD, et al. Salvage total laryngectomy after external-beam radiotherapy: a 20-year experience. *Head Neck* 2016;38 Suppl;1:E1962–E1968.
42. Harada A, Sasaki R, Miyawaki D, et al. Treatment outcomes of the patients with early glottic cancer treated with initial radiotherapy and salvaged by conservative surgery. *Jpn J Clin Oncol* 2015;45:248–255.
43. van der Putten L, de Bree R, Kuik DJ, et al. Salvage laryngectomy: oncological and functional outcome. *Oral Oncol* 2011;47:296–301.
44. Stankovic M, Milisavljevic D, Zivic M, Stojanov D, Stankovic P. Primary and salvage total laryngectomy. Influential factors, complications, and survival. *J BUON* 2015;20:527–539.
45. Gorphe P, Blanchard P, Temam S, Janot F. Influence of the vocal cord mobility in salvage surgery after radiotherapy for early-stage squamous cell carcinoma of the glottic larynx. *Eur Arch Otorhinolaryngol* 2015;272:3013–3018.
46. Wulff NB, Kristensen CA, Andersen E, Charabi B, Sørensen CH, Homøe P. Risk factors for postoperative complications after total laryngectomy following radiotherapy or chemoradiation: a 10-year retrospective longitudinal study in Eastern Denmark. *Clin Otolaryngol* 2015;40:662–671.
47. Reynolds LF, Rigby MH, Trites J, Hart R, Taylor SM. Outcomes of transoral laser microsurgery for recurrent head and neck cancer. *J Laryngol Otol* 2013;127:982–986.
48. Del Bon F, Piazza C, Mangili S, Redaelli De Zinis LO, Nicolai P, Peretti G. Transoral laser surgery for recurrent glottic cancer after radiotherapy: oncologic and functional outcomes. *Acta Otorhinolaryngol Ital* 2012;32:229–237.

49. Han YJ, Lee HS, Kim SW, et al. Transoral laser microsurgery of recurrent early glottic cancer after radiation therapy: clinical feasibility and limitations. *Ann Otol Rhinol Laryngol* 2012;121:375–382.
50. Ansarin M, Planicka M, Rotundo S, et al. Endoscopic carbon dioxide laser surgery for glottic cancer recurrence after radiotherapy: oncological results. *Arch Otolaryngol Neck Surg* 2007;133:1193–1197.
51. Quer M, León X, Orús C, et al. Endoscopic laser surgery in the treatment of radiation failure of early laryngeal carcinoma. *Head Neck* 2000;22: 520–523.
52. Lucioni M, Bertolin A, Lionello M, Giacomelli L, Rizzotto G, Marioni G. Salvage transoral laser microsurgery for recurrent glottic carcinoma after primary laser-assisted treatment: analysis of prognostic factors. *Head Neck* 2016;38:1043–1049.
53. Christiansen H, Hermann RM, Martin A, et al. Long-term follow-up after transoral laser microsurgery and adjuvant radiotherapy for advanced recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2006;65:1067–1074.
54. de Vincentiis M, De Virgilio A, Bussu F, et al. Oncologic results of the surgical salvage of recurrent laryngeal squamous cell carcinoma in a multicentric retrospective series: emerging role of supracricoid partial laryngectomy. *Head Neck* 2015;37:84–91.
55. Viani L, Stell PM, Dalby JE. Recurrence after radiotherapy for glottic carcinoma. *Cancer* 1991;67:577–584.
56. Li M, Lorenz RR, Khan MJ, et al. Salvage laryngectomy in patients with recurrent laryngeal cancer in the setting of nonoperative treatment failure. *Otolaryngol Head Neck Surg* 2013;149:245–251.
57. Hasan Z, Dwivedi RC, Gunaratne DA, Virk SA, Palme CE, Riffat F. Systematic review and meta-analysis of the complications of salvage total laryngectomy. *Eur J Surg Oncol* 2017;43:42–51.
58. Lian TS, Nathan CA. What is the role of flap reconstruction in salvage total laryngectomy? *Laryngoscope* 2014;124:2441–2442.
59. Motamed M, Laccourreye O, Bradley PJ. Salvage conservation laryngeal surgery after irradiation failure for early laryngeal cancer. *Laryngoscope* 2006;116:451–455.

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Oral Cancer Reconstruction Using the Supraclavicular Artery Island Flap: Comparison to Free Radial Forearm Flap

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Purpose: To evaluate whether the pedicled supraclavicular artery island flap (SCAIF) is a sufficient alternative to the fasciocutaneous radial forearm free flap (RFFF) for oral reconstruction in cancer surgery.

Patients and Methods: The authors designed and implemented a retrospective cohort study composed of all consecutive patients who underwent head and neck reconstruction after cancer surgery at their tertiary university hospital from 2013 to 2016. Demographics and peri- and postoperative information were recorded and statistically analyzed.

Results: Of 83 patients who underwent head and neck reconstruction after cancer, 50 were identified as having stage III or IV squamous cell carcinoma of the oral cavity and oropharynx and underwent surgery and reconstruction with the SCAIF (n = 25) or the RFFF (n = 25). Total surgery time (411.0 vs 576.4 minutes; $P < .001$), flap elevation time (39.00 vs 93.78 minutes; $P < .001$), need for intensive care observation (32 vs 96%; $P < .05$), and rate of tracheotomy (64 vs 88%; $P < .05$) were significantly lower in the SCAIF group. There was no statistical difference in the postoperative complication rate or postoperative functional swallowing ability between the 2 groups. Total perioperative costs were significantly lower in patients who underwent reconstruction with the SCAIF (2,621.15 vs 4,453.77€; $P < .01$).

Conclusion: The results of this study suggest that the SCAIF is a straightforward and reliable flap with shorter operative times and comparable outcomes compared with the RFFF.

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Previously, reconstruction of the oral cavity and oropharynx after extensive cancer surgery aimed to reconstruct anatomic defects and decrease postoperative complications. Currently, functional aspects are more and more relevant and at least equivalent. In the past decade, the fasciocutaneous radial forearm free flap (RFFF) has enabled the resection and functional reconstruction of previously inoperable oral

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tumors with good functional outcomes and has become the new workhorse flap in the reconstruction of mucosal defects of the head and neck.[1-3]

One of the challenges of free flap reconstruction is that it requires specialized centers and reconstructive surgeons with microvascular training. It involves a long operative time and more complex postoperative monitoring. In the current era of health care cost containment, greater emphasis is placed on efficiency, improving postoperative outcomes, and lowering overall costs. Because of a demographic shift, patients requiring reconstructive surgery are older with more comorbidities and poor vessel status. This makes them suboptimal candidates for oral reconstruction by a microvascular anastomosed RFFF. Taking these factors into account, axial pedicled regional flaps could be preferred to free flaps in a large proportion of patients because they have a short harvest time and do not require microvascular anastomosis. Nevertheless, the established pedicled flaps in head and neck reconstruction, such as the latissimus dorsi or pectoralis major myocutaneous flap, are not suitable for reconstruction of most oropharyngeal regions. The bulkiness and inflexibility of these flaps make them inferior to the RFFF or other free flaps. The supraclavicular artery island flap (SCAIF) seems to combine the flexibility and volume of an RFFF with the time- and comorbidity-decreasing benefits of a pedicled flap.

The SCAIF is not a new flap, but its anatomy and blood supply were much better understood in 1979 when Lamberty[4] first described it as an axial pedicled flap. It was rarely used during the 1980s and 1990s because of a reported high incidence of necrosis and poor reliability.[5] The interest in its use was revived after Pallua et al[6,7] reported on several successful cases of reconstruction of cervicomental scar contractures. Since then, several studies have reported on the SCAIF as a reliable flap with good postoperative healing capacity when used in oncologic reconstructive surgery and have indicated very good postoperative functional results.[8-11] More recently, investigators have even challenged the supremacy of the RFFF by reporting equivalent or improved outcomes with lower perioperative costs.[12,13]

At their institution, the authors have been using the SCAIF for defects, including the oral cavity and oropharynx, since 2014 with excellent results. During this time, they have identified the advantages offered by this flap. To objectively quantify all the advantages, they directly compared outcomes of reconstructions performed with the SCAIF and RFFF that have taken place at their institution. Thus, the authors hypothesized that shorter operative times and stays in the intensive care unit (ICU) would lower perioperative costs and result in the same or even better postoperative outcomes.

Patients and Methods

PATIENTS AND DATA COLLECTION

The authors retrospectively reviewed the medical records of all consecutive patients who underwent reconstruction of the head and neck region with the SCAIF (n = 51) or RFFF (n = 32) at their institution from January 2013 through June 2016. Inclusion criteria for this study were stage III or IV squamous cancer of the oral cavity or oropharynx and surgery with a primarily curative intent. Patients under palliative care and after salvage surgery were excluded from this study. Patients with recurrent or second primary disease or patients who previously underwent radiation therapy in the head and neck region were included. In total, 50 patients with squamous cancer of the oral cavity or oropharynx who underwent cancer surgery and mucosal reconstruction, with incidentally equivalent-size cohorts (SCAIF, n = 25; RFFF, n = 25), at the Department of Otorhinolaryngology, Head and Neck Surgery, Georg August University (Goettingen, Germany) were included.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Declaration of Helsinki and its amendments or comparable ethical standards. The institutional ehtics committee of the University Medical Center of Goettingen approved this retrospective study (number 22/8/15). For this type of study, formal consent is not required.

Only 2 surgeons (C.W. and M.C.) performed the cancer surgery and reconstruction procedure. These surgeons are trained and experienced microvascular surgeons and frequently perform pedicled and free flap procedures. For the SCAIF flap elevation procedure, the technique was performed as described by Granzow et al.[14] The authors routinely use intraoperative Doppler guidance to find and mark the supraclavicular artery. After measuring the pharyngeal surface that has to be reconstructed and the pedicle length, the flap is elevated distally to proximally and rotated into the pharynx and the required epithelial part is marked. The pedicle is de-epithelialized and the flap is adapted by absorbable sutures. For all patients included in this study, and as a standard in the authors' institution, all SCAIF donor sites were closed primarily and covered with a pressure dressing for at least 1 week. In contrast, RFFF donor sites were routinely closed by a mashed split-thickness skin graft from the anterior thigh and underwent vacuum-assisted therapy for 8 days. Postoperatively, all patients received nutrition through a nasogastric tube for 10 days. Only after inconspicuous barium swallow was the nasogastric tube removed and then an oral diet was initiated.

Table 1. PATIENT DEMOGRAPHICS AND HISTORY

Variable	SCAIF (n = 25)	RFFF (n = 25)	*P* Value
Age (yr), mean ± SD	68.9 ± 10.6	61.5 ± 7.1	.01
Gender, n (%)			
Men	19 (76)	22 (88)	.274
Women	6 (24)	3 (12)	
Follow-up (mo), mean ± SD	6.9 ± 6.6	22.8 ± 19.4	
Previous HNSCC, n (%)	2 (8)	2 (8)	
Previous CRT, n (%)	2 (8)	0 (0)	
pTNM, n (%)			
T2	4 (16)	2 (8)	.848
T3	16 (64)	19 (76)	
T4	5 (20)	4 (16)	
N0	8 (32)	6 (24)	.496
N1	1 (4)	8 (32)	
N2	15 (60)	10 (40)	
N3	1 (4)	1 (4)	
UICC stage, n (%)			
III	8 (32)	12 (48)	>.05
IV	17 (68)	13 (54)	

Abbreviations: CRT, chemoradiation; HNSCC, head and neck squamous cell carcinoma; RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap; SD, standard deviation; UICC, Union for International Cancer Control.

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Medical records and computer-based documentations were used for data collection. Demographic data, history of head and neck cancer, previous chemoradiation, and TNM classification were recorded for each patient (Table 1). Despite advanced tumor staging with spread in different areas of the oropharynx and oral cavity, primary tumor localization was subdivided (Table 2).

All perioperative data, including flap size, performed tracheotomy, operating room times, and length of ICU stay, were recorded and compared between the 2 groups. For analysis, preoperative workup time (defined as time from operating room entrance to incision), total surgery time (defined as time from incision until leaving the operating room), flap procedure time (estimated time from beginning with elevation to wound closure), and harvesting time (estimated time of flap elevation) were noted by the nursing stuff and were transferred to the medical record. ICU stay was documented in an institutional database.

Postoperative information, including recipient site complications, donor site complications, length of stay, and follow-up, were extracted from medical records. The authors distinguished minor complications, which included every complication that could be managed conservatively, from major complications, which required an operative intervention. Minor complications included small flap dehiscences, small fistulas, and partial necrosis (<30% of volume). Major complications included partial necrosis with necronectomy, microvascular revisions, and total flap loss (TFL). Donor site complications involved the shoulder for patients receiving the SCAIF or the radial forearm for patients receiving the RFFF. Functional data were collected for all patients, including postoperative barium swallow test results.

COST ANALYSIS

For cost analysis, only costs associated with the operative procedure and the postoperative ICU stay were included (ie, perioperative costs). Other costs, such as intraoperative materials, intraoperative and postoperative pathology and pathologists, normal ward stay, and adjuvant therapy, were excluded because they were almost identical and thus did not influence the statistical comparison. Personal

Table 2. TUMOR LOCALIZATION

Localization	SCAIF, n (%)	RFFF, n (%)
Tonsil, soft palate, pharynx	11 (44)	9 (36)
Tongue base, tongue body	7 (28)	7 (28)
Lateral edge of tongue	7 (28)	9 (36)
Total	25 (100)	25 (100)

Abbreviations: RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap.

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Table 3. TEAMS AND COST CALCULATIONS

Type of Reconstruction	Medical Professionals	n	Wage/hr (€)	Costs/hr (€)
SCAIF				
	(Flap) surgeon	1	41.80	
	Surgeon (resident)	1	26.41	
	Nurse (OP)	2	21.51	
	Anesthesiologist (ANA)	1	26.41	
	Nurse (ANA)	1	12.25	
			→	128.40
RFFF				
Total surgery time	(Flap) surgeon	1	41.80	
	Surgeon (resident)	1	26.41	
	Nurse (OP)	2	21.51	
	Anesthesiologist (ANA)	1	26.41	
	Nurse (ANA)	1	12.25	
			→	128.4
Flap procedure time	(Flap) surgeon	1	41.80	
	Surgeon (resident)	1	26.41	
	Nurse (OP)	1	21.51	
			→	89.72

Abbreviations: ANA, anesthesiology; OP, operating room nurse; RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap.

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costs were calculated after identifying the average hourly wage of every medical professional taking part in the procedure (consultants, residents, and nurses). Depending on the procedure, different personnel were needed intraoperatively. There were different teams for the SCAIF and RFFF operations, which were included in the overall calculation. Teams and average hourly wages are presented in Table 3. The institutional accounts department calculated the costs for an ICU stay at 65.50€ per hour, which was multiplied by the recorded stay in hours of each patient.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 23 (IBM GmbH, Ehningen, Germany). Before comparing the SCAIF and RFFF groups, all parameters and variables were tested for normal distribution by the Kolmogorov-Smirnov goodness-of-fit test. Equality of variances was assessed by the Levene test. Depending on these results, differences between the 2 groups were tested by performing the unpaired 2-sided Student *t* test or the nonparametric Mann-Whitney *U* test. Differences were considered significant at *P* values less than .05 before statistical analysis.

Results

From January 2013 through June 2016, 83 consecutive head and neck reconstructions with the SCAIF or RFFF were performed by the first author (C.W.) and co-author (M.C.). After applying the inclusion criteria over this 3-year period, 50 patients with advanced head and neck squamous cell carcinoma (HNSSC) of the oral cavity or oropharynx who underwent reconstruction using the SCAIF (n = 25) or RFFF (n = 25) were identified. Follow-up time ranged from

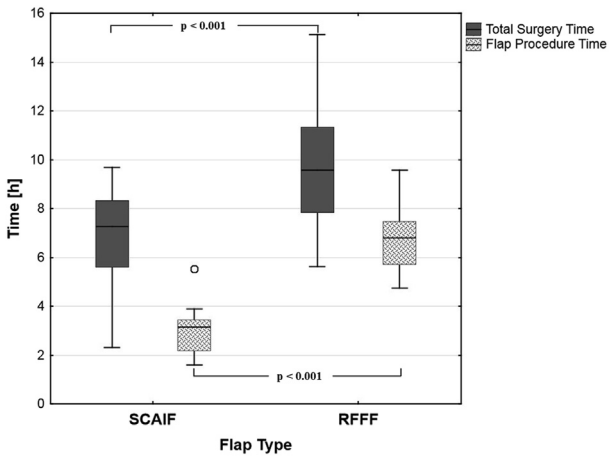

FIGURE 1. Comparison of total surgery time and flap procedure time. Standard boxplots (lower quartile, median, upper quartile) are used to illustrate the results in the SCAIF group (total surgery time, n = 25; flap procedure time, n = 14) and the RFFF group (n = 25). *Dots* denote mild statistical outliers (interquartile range, 1.5 to 3 times). RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap.

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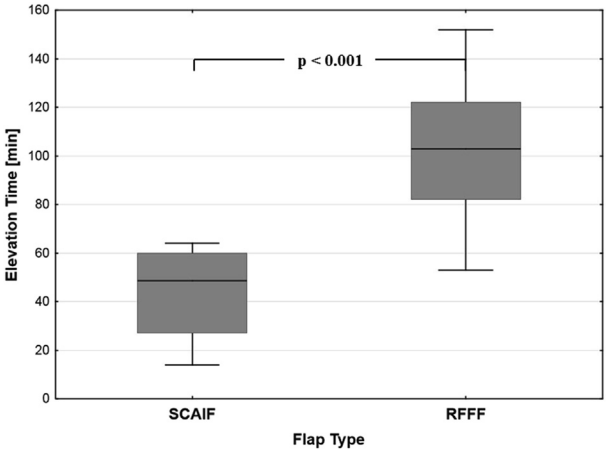

FIGURE 2. Flap elevation time (minutes). Standard boxplots (lower quartile, median, upper quartile) are used to illustrate the results. Mean elevation times were 39.0 ± 10.00 minutes for the SCAIF and 93.78 ± 28.6 minutes for the RFFF. RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap. *P* <.001

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10 days to 13 months (6.0 ± 6.9 months) in the SCAIF group and from 3.4 months to 3.5 years (22.8 ± 19.4 months) in the RFFF group.

PATIENT DEMOGRAPHICS AND HISTORY

Analysis of patient demographics and history (Table 1) showed a notable age difference between the 2 cohorts. The mean age of patients in the SCAIF group was 68.9 years and that in the RFFF group was 61.5 years ($P < .05$). There was a male predominance in the 2 cohorts and no statistical difference between them (76% of SCAIF group vs 88% of RFFF group; $P = .274$). A history of HNSCC (local recurrence) was recorded in 8% of cases in the 2 groups. In the SCAIF cohort, 2 patients (8%) had a history of chemoradiotherapy. Tumor localization (Table 2) and distribution of pTNM classification were well balanced between the cohorts and did not differ significantly ($P = .848$ for tumor stage; $P = .496$ for nodal stage).

PERIOPERATIVE DATA

Analysis showed that the rate of tracheotomy was significantly lower for the SCAIF group versus the RFFF group (64 vs 88%; $P < .05$). Total surgery time was significantly shorter in the SCAIF group (411.0 vs 576.4 minutes; $P < .001$; Fig 1). Flap procedure time for the SCAIF was 122.0 ± 21.4 minutes (mean ± standard deviation; n = 14), and performing the RFFF took 409.2 ± 83.20 minutes (n = 25). There was a marked statistically significant difference when comparing these durations ($P < .001$). Flap elevation time also showed a marked statistically significant difference ($P < .001$). Mean SCAIF elevation time was 39.00 ± 10.00 minutes and mean RFFF elevation time was 93.78 ± 28.6 minutes (Fig 2, Table 4).

In addition to operation times, the need for an ICU stay and length of ICU stay were compared between the 2 groups. Eight of 25 patients in the SCAIF group required ICU monitoring postoperatively compared with 24 patients (96%) in the RFFF group ($P < .001$; Table 4). When ICU observation was necessary postoperatively, the length of stay was significantly shorter in the SCAIF group compared with the RFFF group (24.3 ± 61.2 vs 36.8 ± 26.5 hours; $P < .05$).

POSTOPERATIVE DATA

Statistical analysis of overall complications of the recipient site between the 2 groups showed no significant difference ($P = .547$). Seven patients in the SCAIF group and 8 patients in the RFFF group developed complications at the recipient site.

Table 4. PERIOPERATIVE DATA

Variable	SCAIF (n = 25)	RFFF (n = 25)	*P* Value
Tracheotomy, n (%)	16 (64)	22 (88)	<.05
Minimum operation time, mean ± SD			
Preoperative workup	61.6 ± 23.5	58.4 ± 17.6	.12
Total surgery time	411.0 ± 119.05	576.4 ± 144.17	<.001
Flap procedure time	122.0 ± 21.4*	409.2 ± 83.20	<.001
Elevation time	39.00 ± 10.00*	93.78 ± 28.6	<.001
ICU stay—yes, n (%)	8 (32)	24 (96)	<.001
ICU stay (hr), mean ± SD	24.3 ± 61.2	36.8 ± 26.5	<.05
Flap size (cm^2), mean ± SD	26.5 ± 5.6	34.0 ± 9.8	

Abbreviations: ICU, intensive care unit; RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap; SD, standard deviation.

* n = 14.

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Table 5. FREQUENCY OF POSTOPERATIVE COMPLICATIONS

Variable	SCAIF (n = 25), n (%)	RFFF (n = 25), n (%)	*P* Value
Complications at recipient site	7 (28)	8 (32)	.547
Minor	4 (16)	1 (4)	<.05
Major/total flap loss	3 (12)/1 (4)	7 (28)/3 (12)	<.05
Complications at donor site	10 (40)	10 (40)	.708
Minor	8 (32)	8 (32)	
Major	2 (8)	2 (8)	

Abbreviations: RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap.

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When major and minor complications were compared separately, patients with SCAIF reconstruction showed significantly fewer major complications but significantly more minor complications ($P < .05$; Table 5).

The most frequent minor complication in the SCAIF group was a fistula (n = 3) detected by barium swallow, which was routinely performed on postoperative day 10. In the RFFF group, 3 TFLs (12%) were recorded, whereas 1 TFL (4%) occurred in the SCAIF group. Two of 25 patients (8%) in the SCAIF cohort developed partial flap necrosis (PFN), which required necronectomy under total anesthesia.

For complications of the donor site, the overall comparison and the comparison of major and minor complications showed no statistically significant difference ($P = .708$). In the SCAIF group, 2 patients (8%) developed a major complication. These 2 patients had impaired wound healing with dehiscence at the critical acromial shoulder region. In these cases 3 months after primary surgery, a small rotational skin flap was successfully performed. Table 6 lists all complications of the recipient and donor sites by name and frequency. Mean length of hospital stay in the 2 groups was 28 days and did not show a significant difference ($P = .89$).

FUNCTIONAL POSTOPERATIVE DATA

A barium swallow was routinely used 2 weeks after the operation to assess the functional ability of patients. Four patients (16%) in the RFFF group and 6 (24%) in the SCAIF group showed a tendency to aspirate. There was no statistical difference between the 2 groups ($P = .63$). These patients were supported with regular swallowing therapy after discharge.

COST ANALYSIS

As described in the Patients and Methods section, different teams of surgeons and nurses were needed for the SCAIF and RFFF procedures (Table 3), and costs for 1 hour of SCAIF reconstruction were estimated at 128.40€. For RFFF operations, 128.4 plus 89.72€ per hour during the flap procedures was included in the personal cost calculations. In summary, mean total personal costs for each operation were 1,026.58 ± 303.54€ in the SCAIF group versus 2,044.76 ± 463.69€ in the RFFF group. Statistical analysis (Fig 3) showed a marked significant difference ($P < .001$). Total perioperative costs (personal costs plus ICU costs) for 1 patient of the SCAIF group was 2,621.15 versus 4,453.77€ for 1 patient in the RFFF

Table 6. PATTERN OF COMPLICATIONS

Complication	SCAIF (n = 25)	n (%)	RFFF (n = 25)	n (%)
Major at recipient site (managed by revision)	Partial necrosis with necronectomy	2 (8)	Flap vessel occlusion	3 (12)
	Total flap loss	1 (4)	Total flap loss	3 (12)
			Flap dehiscence	1 (4)
Minor at recipient site	Fistula	3 (12)	Fistula	1 (4)
	Partial necrosis	1 (4)		
Major at donor site	Dehiscence	2 (8)	Postoperative bleeding	1 (4)
			Necrosis	1 (4)
Minor at donor site	Dehiscence	7 (28)	Impaired wound healing	4 (12)
	Necrosis	1 (4)	Partial necrosis	4 (12)

Abbreviations: RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap.

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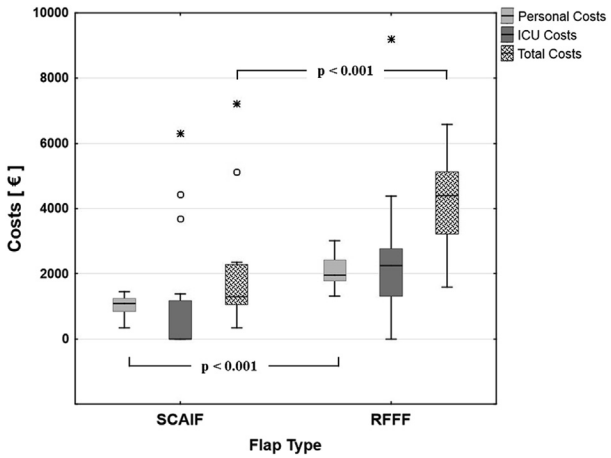

FIGURE 3. Cost analysis. Standard boxplots (lower quartile, median, upper quartile) are used to illustrate the results in the SCAIF group (n = 25) and RFFF group (n = 25). *Dots* denote mild statistical outliers (interquartile range, 1.5 to 3 times). *Asterisks* denote extreme statistical outliers (>3 times interquartile range). ICU, intensive care unit; RFFF, radial forearm free flap; SCAIF, supraclavicular artery island flap.

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group ($P < .001$). This represents a cost increase of 1.7 times in the RFFF group.

Discussion

In this study, the authors retrospectively compared a wide range of peri- and postoperative outcomes of patients with advanced HNSCC of the oral cavity or oropharynx undergoing mucosal defect reconstruction using the SCAIF (n = 25) or RFFF (n = 25). To the authors' knowledge, only 2 other publications have compared SCAIF and free flap outcomes. Granzow et al[12] and Kozin et al[13] compared the SCAIF with the RFFF and anterolateral thigh flap for different indications (temporal bone, pharynx, or cutaneous defect reconstruction) and different patients (oncologic and traumatic). This is the first study comparing the SCAIF exclusively with the RFFF for a single indication.

Patients in the SCAIF group were markedly older than patients in the RFFF group (68.9 vs 61.5 yr). Although the authors tried to narrow the difference by matching the 2 groups, this was a retrospective study, which is susceptible to selection bias. In general, the authors did not preselect the patients and included consecutively performed reconstructions of the oral cavity or oropharynx. The age difference can be explained by the use of the SCAIF as a reconstruction modality in patients with a poor vascular status, pathologic Allen test result, or serious comorbidities that occur more frequently in older patients.

The present results indicate equal or fewer postoperative complications in the SCAIF group compared with the RFFF group, which are comparable to those previously reported in the literature.[12,13]

There were fewer major recipient site complications and 1 TFL in the SCAIF group (4%). With a major recipient site complication rate of 12% (8% PFNs, 4% TFLs), the present results are totally in line with the literature.[8,10,15-17]

In the 2 cohorts, 10 of 25 patients developed donor site complications, with most (>90%) being minor complications. This rate is equal or a bit higher than that reported in the literature.[9,18,19] There were 2 major donor site complications in the SCAIF group, which involved impaired wound healing with dehiscence at the critical acromial shoulder region. In these cases, a small rotational skin flap was successfully performed achieving good wound healing.

This study, which included only patients with stage III or IV squamous cancer of the oral cavity or oropharynx, identified good postoperative functional results. Postoperative swallowing ability according to barium swallow results appeared to be similar between the 2 groups.

In this study, there was a marked difference in tracheotomy rates. Patients undergoing reconstruction with the RFFF were more likely to receive a tracheotomy (88%) compared with the SCAIF group (64%). This is another noteworthy finding because the presence of a tracheotomy can prolong hospital stay, is associated with a decrease in mental health postoperatively, and is known to worsen self-esteem.[20] The authors do not have a clear explanation for this finding, because the cohorts were well matched by TNM classification and tumor localization. They presume that the lower tracheotomy rate in the SCAIF cohort is the result of a shorter procedure and less manipulation at the recipient site. Nevertheless, a departmental bias toward a tracheotomy for patients receiving free tissue transfer cannot be ruled out.

There was a marked difference in the follow-up period of patients undergoing the RFFF versus SCAIF procedure. This is due to the fact that in their institution, the authors started performing SCAIF reconstructions frequently only since 2014. Before 2014, free flaps were used primarily to reconstruct the oropharynx or oral cavity.

One of the most noteworthy results of this study was identified after analyzing the operation times. Total surgery time was considerably shorter in the SCAIF group (411.0 vs 576.4 minutes). The single team performing the SCAIF surgery saved time from the absence of an anastomosis and a shorter elevation time. These results are in line with the literature, where shorter total surgery times and elevation times shorter than 60 minutes are frequently reported.[19,21-24] The authors consider

this to be a very important contributing factor in the postoperative course, because it associated with fewer ICU admissions and overall lower costs.

ICU admissions and time spent in an ICU were considerably decreased in the SCAIF group. The authors presume that this has to do with a shorter operative time and the traditional view among reconstructive surgeons that patients need to be closely monitored postoperatively after receiving the RFFF.

In the current era, health care systems are on the brink of failure because of increasing costs and increasing demands for efficiency. After comparing the perioperative costs of reconstructions using the SCAIF versus the RFFF, reconstructions using the RFFF increased the cost 1.7 times more.

Patients had a longer ward stay compared with what is usually reported in the literature after reconstruction using the SCAIF or RFFF.[13] This is attributed to 2 important factors. First, many patients had a very low socioeconomic status, with residential problems. The authors always aim to address these issues before discharge, resulting in extended hospitalizations. Second, postoperative management of all patients includes nasogastric tube feeding in the first 10 postoperative days, extensive tooth sanitation, and presentation to the department of radiotherapy before discharge.

The major limitation of this study is its retrospective nature that inherently has biases. Another limitation is that the authors did not routinely assess postoperative quality of life for these patients. They have incorporated this in their practice and their future results will include patients' perceptions of reconstructive surgery.

In conclusion, the ideal flap for reconstructive oncology procedures should restore the form and function of the defect in a single-stage procedure, be reliable and straightforward to harvest, save time, lower costs, and have no donor site comorbidity. Such an ideal flap does not exist, but the SCAIF appears to satisfy most of these criteria. It is ideal when treating patients with many comorbidities and poor vascular status. It is thin and pliable and can be used for complex reconstructions of the oropharynx, making it equivalent to the RFFF and superior to other pedicled flaps. Moreover, as shown in this study, it has equivalent or even improved postoperative outcomes and is associated with lower rates of tracheotomy, fewer ICU admissions, and substantially lower costs. In the authors' institution, use of the SCAIF has increased dramatically in the past 2 years. It is a reliable alternative to the RFFF and appears to be even superior when reconstruction for patients with serious comorbidities is needed.

References

1. Cannady SB, Rosenthal EL, Knott PD, et al: Free tissue transfer for head and neck reconstruction: A contemporary review. JAMA Facial Plast Surg 16:367, 2014
2. Welkoborsky HJ, Deichmuller C, Bauer L, et al: Reconstruction of large pharyngeal defects with microvascular free flaps and myocutaneous pedicled flaps. Curr Opin Otolaryngol Head Neck Surg 21:318, 2013
3. Avery CM: Review of the radial free flap: Is it still evolving, or is it facing extinction? Part one: Soft-tissue radial flap. Br J Oral Maxillofac Surg 48:245, 2010
4. Lamberty BG: The supra-clavicular axial patterned flap. Br J Plast Surg 32:207, 1979
5. Blevins PK, Luce EA: Limitations of the cervicohumeral flap in head and neck reconstruction. Plast Reconstr Surg 66:220, 1980
6. Pallua N, Machens HG, Rennekampff O, et al: The fasciocutaneous supraclavicular artery island flap for releasing postburn mentosternal contractures. Plast Reconstr Surg 99:1878, 1997
7. Pallua N, Magnus Noah E: The tunneled supraclavicular island flap: An optimized technique for head and neck reconstruction. Plast Reconstr Surg 105:842, 2000
8. Chiu ES, Liu PH, Friedlander PL: Supraclavicular artery island flap for head and neck oncologic reconstruction: Indications, complications, and outcomes. Plast Reconstr Surg 124:115, 2009
9. Teymoortash A, Mandapathil M, Hoch S: Indications for reconstruction of mucosal defects in oropharyngeal cancer using a supraclavicular island flap. Int J Oral Maxillofac Surg 43:1054, 2014
10. Kokot N, Mazhar K, Reder LS, et al: The supraclavicular artery island flap in head and neck reconstruction: Applications and limitations. JAMA Otolaryngol Head Neck Surg 139:1247, 2013
11. Herr MW, Bonanno A, Montalbano LA, et al: Shoulder function following reconstruction with the supraclavicular artery island flap. Laryngoscope 124:2478, 2014
12. Granzow JW, Suliman A, Roostaeian J, et al: Supraclavicular artery island flap (SCAIF) vs free fasciocutaneous flaps for head and neck reconstruction. Otolaryngol Head Neck Surg 148: 941, 2013
13. Kozin ED, Sethi RK, Herr M, et al: Comparison of perioperative outcomes between the supraclavicular artery island flap and fasciocutaneous free flap. Otolaryngol Head Neck Surg 154:66, 2016
14. Granzow JW, Suliman A, Roostaeian J, et al: The supraclavicular artery island flap (SCAIF) for head and neck reconstruction: Surgical technique and refinements. Otolaryngol Head Neck Surg 148:933, 2013
15. Sandu K, Monnier P, Pasche P: Supraclavicular flap in head and neck reconstruction: Experience in 50 consecutive patients. Eur Arch Otorhinolaryngol 269:1261, 2012
16. Vinh VQ, Van Anh T, Ogawa R, et al: Anatomical and clinical studies of the supraclavicular flap: Analysis of 103 flaps used to reconstruct neck scar contractures. Plast Reconstr Surg 123:1471, 2009
17. Razdan SN, Albornoz CR, Ro T, et al: Safety of the supraclavicular artery island flap in the setting of neck dissection and radiation therapy. J Reconstr Microsurg 31:378, 2015
18. Su T, Pirgousis P, Fernandes R: Versatility of supraclavicular artery island flap in head and neck reconstruction of vessel-depleted and difficult necks. J Oral Maxillofac Surg 71:622, 2013
19. Zhang B, Yan D, Zhang Y, et al. Clinical experience with the supraclavicular flap to reconstruct head and neck defects. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 50:468, 2015 (in Chinese)
20. Hashmi NK, Ransom E, Nardone H, et al: Quality of life and self-image in patients undergoing tracheostomy. Laryngoscope 120(suppl 4):S196, 2010
21. Alves HR, Ishida LC, Ishida LH, et al: A clinical experience of the supraclavicular flap used to reconstruct head and neck defects

in late-stage cancer patients. J Plast Reconstr Aesthet Surg 65: 1350, 2012
22. Anand AG, Tran EJ, Hasney CP, et al: Oropharyngeal reconstruction using the supraclavicular artery island flap: A new flap alternative. Plast Reconstr Surg 129:438, 2012
23. Giordano L, Di Santo D, Occhini A, et al: Supraclavicular artery island flap (SCAIF): A rising opportunity for head and neck reconstruction. Eur Arch Otorhinolaryngol 273:4403, 2016
24. Liu PH, Chiu ES: Supraclavicular artery flap: A new option for pharyngeal reconstruction. Ann Plast Surg 62:497, 2009