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Predictors and determinants for recovery and survival after upper abdominal surgery

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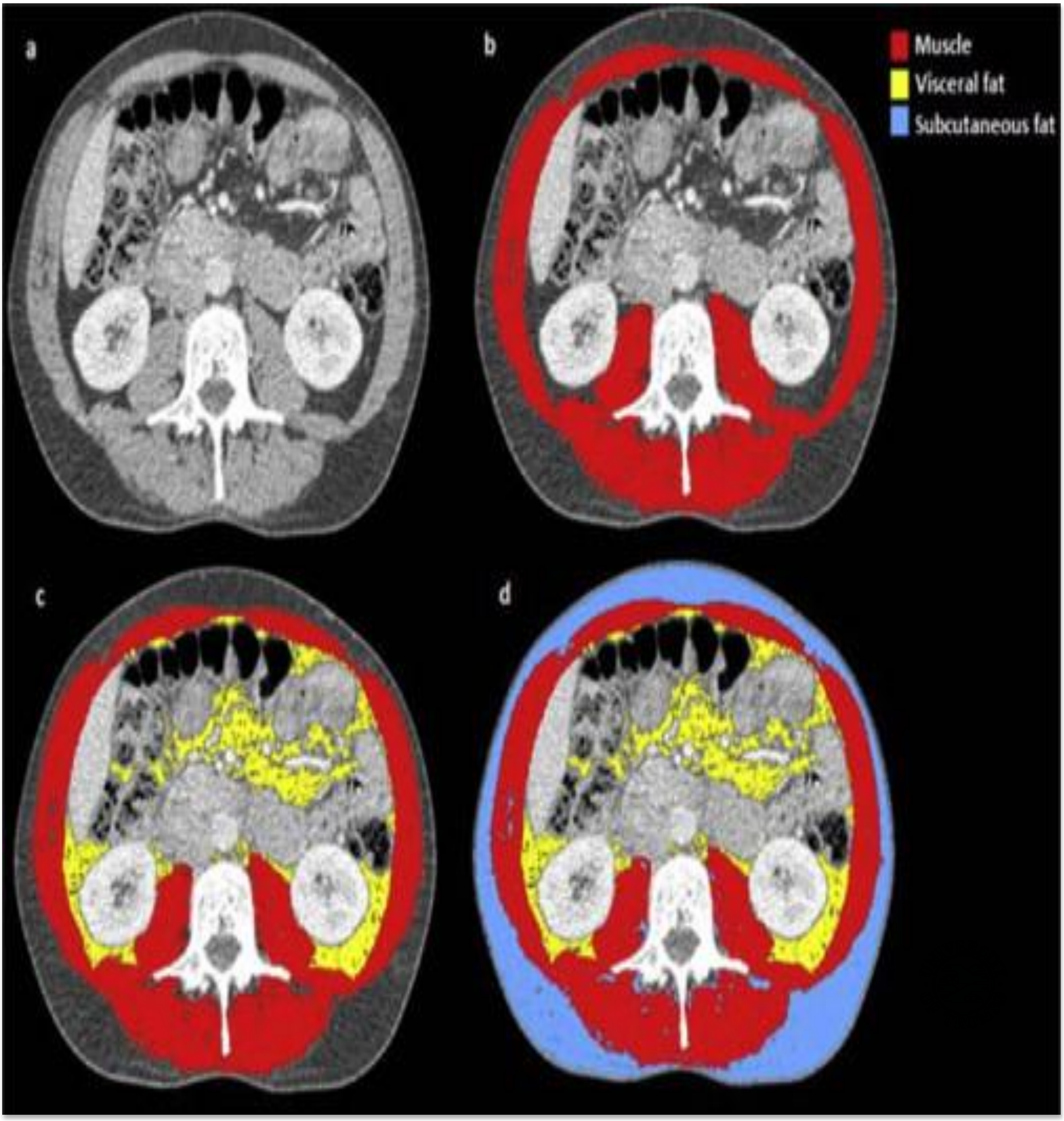

PREDICTORS AND DETERMINANTS FOR RECOVERY AND SURVIVAL AFTER UPPER ABDOMINAL SURGERY

"*The turning point:* This period of convalescence has been recognized by surgeons for many centuries. At present, interns and residents state that women at this period of convalescence show a "positive lipstick sign", meaning that the patient now takes renewed interest in her surroundings. She turns a corner toward recovery".

- Francis D. Moore, North-American surgeon and convalescence researcher, describing recovery after surgery in 1958 (1).

Illustration on the front page: Body composition analyses from a computed tomography image (2).

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LIST OF PAPERS

Paper I

Aahlin EK, Meyenfeldt M, Dejong CHC, Ljungqvist O, Fearon KC, Lobo DN, Demartines N, Revhaug A, Wigmore SJ, Lassen K: Functional recovery is considered the most important target: a survey of dedicated professionals. Perioperative Medicine 2014 (3)

Paper II

Hughes M, Coolsen MME, Aahlin EK, Harrison EM, McNally SJ, Dejong CHC, Lassen K, Wigmore SJ: Attitudes of patients and care providers for enhanced recovery after surgery programs after major abdominal surgery. Journal of Surgical Research 2014 (4)

Paper III

Aahlin EK, Tranø G, Johns N, Horn A, Søreide JA, Fearon KC, Revhaug A, Lassen K: Risk factors, complications and survival after upper abdominal surgery: a prospective cohort study. BMC Surgery 2015 (5)

Paper IV:

Aahlin EK, Tranø G, Johns N, Horn A, Søreide JA, Fearon KC, Revhaug A, Lassen K: Health-related quality of life, cachexia and overall survival after major upper abdominal surgery: a prospective cohort study. Scandinavian Journal of Surgery 2016 (6)

Paper V

Aahlin EK, Irino T, Johns N, Brismar TB, Nilsson M, Revhaug A, Lassen K: Body composition indices and tissue loss in patients with resectable gastric adenocarcinoma. Manuscript in preparation

Paper VI

Aahlin EK, Olsen F, Uleberg B, Jacobsen BK, Lassen K: Major postoperative complications are associated with impaired long-term survival after gastro-esophageal and pancreatic cancer surgery: a complete national cohort study. BMC Surgery 2016 (7).

SELECTED ABBREVIATIONS

- ERAS: Enhanced Recovery after Surgery
- ERP: Enhanced recovery program
- WL: Weight loss
- CT: Computed tomography
- BMI: Body mass index
- SMT: Skeletal muscle tissue
- VAT: Visceral adipose tissue
- SAT: Subcutaneous adipose tissue
- HRQOL: Health-related quality of life
- SF 36: Short form 36
- PCS: Physical component summary
- MCS: Mental component summary

GLOSSARY

- Upper abdominal surgery: Gastroesophageal and hepatopancreaticobiliary surgery.
- Enhanced recovery programs: Concepts based upon protocols of evidence-based care items applied perioperatively to achieve optimal stress reduction following surgery (8)
- Body composition analyses: Analyses of the amount of fat and lean tissue in the human body (9).
- Cancer cachexia: Multifactorial syndrome with ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism (10).
- Appendicular skeletal mass: Skeletal muscle tissue from arms and legs (9).
- Lean tissue: Body tissue without fat and bone mineral (9).
- Myopenia or sarcopenia: Low relative amount of skeletal muscle tissue or loss of skeletal muscle tissue (used in both contexts). Both terms lack universally accepted definitions and cut-offs (9;11).
- Myosteatosis: Fatty infiltration in skeletal muscle tissue (12).
- Sarcopenic obesity: The combination of sarcopenia and obesity (12).

1. INTRODUCTION

Patients with colorectal malignancies have benefited from major improvements in surgical technique and perioperative care during the last decades. These improvements have contributed to better prognosis and faster recovery, with five-year survival around 80% for localized colorectal cancer and reports of discharge from hospital within 24 hours after colon resections.

In contrast, patients with upper abdominal malignant disease often experience delayed recovery and long-standing functional impairment. Postoperative complications are frequent and the prognosis is often poor. Only a small fraction of patients will survive for five years or more after surgery. Delayed recovery, postoperative morbidity and poor prognosis will naturally affect patients' health-related quality of life (HRQOL).

Upper abdominal malignancies are often associated with cachexia and patients are often weakened preoperatively, characterized by extensive weight loss, abnormal serum-albumin and sarcopenia (low relative amount of skeletal muscle tissue). This may contribute to delayed recovery, increased morbidity, reduced HRQOL and ultimately reduced survival.

Improved survival is an essential objective in upper abdominal surgery. Enhanced recovery, reduced morbidity and improved HRQOL are important in itself, but it may also lead to improved survival.

Improvements in recovery and survival after upper abdominal surgery relies on high-quality research. While overall survival is a robust and objective outcome measure in clinical research, recovery is much more difficult to define.

Avoidance of postoperative morbidity is crucial for achieving enhanced recovery. Recent reports have also indicated that reduction of postoperative morbidity may also lead to improved long-term survival, even for patients initially surviving the double hit of major surgery and postoperative complications.

This thesis aims to explore predictors and determinants for recovery and survival after upper abdominal surgery. It aims to explore how patients and dedicated professionals define recovery. Furthermore, it aims to explore new and old indicators of risk and prognosis with emphasis on methods to assess cachexia and sarcopenia. Finally, it aims to explore correlations between postoperative morbidity, HRQOL and overall survival after major upper abdominal surgery.

2. BACKGROUND

2.1 Upper abdominal surgery

Upper abdominal surgery is very often associated with postoperative complications and longstanding functional impairment (13;14). Survival after surgery for upper abdominal malignancies, even after operations with curative intent, is often limited (15;16). Patients with upper abdominal malignancies are often weakened by cachexia and sarcopenia (low muscle mass) (17;18). Both cachexia and sarcopenia have been associated with postoperative complications and reduced survival (2;19-22). Strict evaluation of surgical risk and benefit is essential in upper abdominal surgery.

Systematic follow-up is essential after colorectal cancer resections since metastatic disease can be treated with curative intent (23). Little survival benefit has been shown from strict oncologic follow-up after upper abdominal cancer surgery (24;25). There is a need to find other ways to improve long-term survival. Patients with upper abdominal malignancies may be offered adjuvant oncological therapy, sometimes with limited benefit and unwanted side effects (26-28). Patients and surgeons often face difficult decisions in upper abdominal surgery, which make postoperative assessment of expected survival especially important.

2.2 Recovery

Enhanced recovery concepts are based upon protocols of evidence-based care items applied perioperatively to achieve optimal stress reduction following surgery with subsequent reductions in morbidity and accelerated recovery (8). Traditionally, it has been considered that all protocol items are equally important and that synergistic effects on recovery are optimal only when all items are implemented (8;29). These views have lately been challenged as some items are seen as outdated and others as standard of care.

Francis D Moore defined surgical convalescence in 1958 in the following way (1): "Convalescence includes all the interlocking physical, chemical, metabolic, and psychological factors commencing with the injury, or even slightly before the injury, and terminating only when the individual has returned to normal physical well-being, social and economic usefulness, and psychological habitus." Whilst FD Moore half a century ago focused on the importance of functional recovery, the length of hospital stay (LOS) has been the dominant outcome in convalescence research in later years (30).

High-quality research on surgical convalescence may lead to improved outcome for our patients, but an essential first step in such research development is international consensus on definitions, objectives and means (30).

2.3 Risk assessment: Cachexia and sarcopenia

Preoperative weight loss has been associated with increased postoperative mortality since North-American surgeon Hiram Studley's paper on patients operated for peptic ulcer in 1936 (31). Abnormal serum-albumin has been associated with unfavorable postoperative outcome for more than a decade (32;33). An involuntary weight loss of five percent or more has been recognized to be associated with reduced survival for more than thirty years (34) and it has been proposed as a diagnostic criterion for cancer cachexia (10).

Sarcopenia has been associated with postoperative complications and reduced survival after cancer surgery (2;19-22), but the results have been somewhat conflicting (18;35;36). Sarcopenia has also been associated with increased chemotherapy-associated toxicity and decreased time to tumor progression in patients receiving palliative chemotherapy (37). In contrast, sarcopenia has also been linked to increased pathological response and progression-free survival in patients receiving neoadjuvant chemotherapy (38). While visceral adiposity has been associated with diabetes and diabetes again has been associated with unfavorable outcome after surgery, evaluations of a direct association between adipose tissue indices and unfavorable outcome have shown conflicting results (39-41). Most recently, sarcopenia has been associated with pulmonary complications after esophagectomies (42) and the combination of low muscularity and visceral obesity has been linked to increased occurrence of pancreatic fistulas after pancreaticoduodenectomies (43;44). A recent study investigated obesity, sarcopenia and outcome after colorectal resections within an enhanced recovery program. While isolated obesity or sarcopenia was not associated with increased morbidity or mortality, a dramatic increase in mortality was observed in patients with the combination of both (sarcopenic obesity) (12).

An ongoing loss of both skeletal muscle and adipose tissue during neoadjuvant chemotherapy treatment for both gastric and pancreatic cancer has been shown (35;36). Still, such loss has not been consistently linked to either complications or survival (35;36). Extensive loss of skeletal muscle and adipose tissue during adjuvant treatment for gastric adenocarcinoma has also been described, but such loss has – again - yet to be linked to clinical outcome (45). Most recently, loss of skeletal muscle tissue after colorectal cancer resections has been observed in a large cohort and minimally invasive surgery seems to protect against such loss (46).

Analyses of body composition, weight loss and serum-albumin

Three different methods for assessing skeletal muscle tissue on preoperative CT images has emerged in the recent years; the measurement of lumbar skeletal muscle index, the total psoas muscle area or the total psoas muscle volume (47-49). Many different cut-offs have been presented, some almost identical to others, and many have not been validated in other studies (20;47;50;51).

Assessment of preoperative weight loss depends on patients' recollection of pre-morbid weight, which might be inaccurate. Serum-albumin can be influenced by many factors such as nutrition, dehydration and inflammation and therefore hard to interpret (52). Therefore, supplementary tools are needed in both research and clinical practice (10). Since almost all patients subjected to upper abdominal surgery will be examined with at least one preoperative CT scan for diagnostic and staging purposes, CT-based body composition indices may represent an opportunity for new risk and prognosis assessment tools. There is increasing evidence that sarcopenia might be an indicator of poor prognosis, independent of disease stage in some malignancies (22;49). Suggestions of genetic risk factors and potential therapeutic interventions (19) for such sarcopenia is especially interesting. Still, further validation of both methods and disease-specific cut-offs are warranted.

2.4 Self-reported health-related quality of life

Measurement of patient reported outcome measures (PROM), especially self-reported health-related quality of life (HRQOL) is often considered an essential part of clinical research (53;54). Measurement of HRQOL may demand significant resources as some instruments (questioners) are time-consuming, both for patients, researchers and clinicians. Many different disease specific and unspecific instruments exist. There is a huge variation in the amount of validation and evidence supporting the instruments in use (55). An important aspect of the validation needed is to establish disease-specific correlations with other important prognosis indicators and outcome measures.

Reduced pretreatment HRQOL have been clearly linked to reduced survival (53). Less is known about the relationship between *post*operative HRQOL and survival after abdominal surgery, although some studies have indicated a positive association (56). While weight loss has been associated with reduced HRQOL (54), less is known about the impact of sarcopenia on HRQOL in upper abdominal surgery (57).

Postoperative prognosis assessment is important, as information on disease stadium from the histopathological examination is more usually much more accurate than information obtained from preoperative examinations. In addition, patients often face difficult decisions after surgery (e.g. whether to receive adjuvant chemotherapy).Research has indicated that oncologic follow-up including routine imaging can cause increased anxiety (58) but many patients welcome regular visits to a physician (59). Postoperative physical HRQOL is probably influenced by many factors and stage of the disease might be the most important. Nevertheless, postoperative HRQOL is also influenced by factors which are not necessarily directly related to the stage of disease, including functional impairment, pain and nutritional depletion. If a relationship between postoperative HRQOL and survival can be validated, further research might reveal factors that could improve survival with very few unwanted side effects.

2.5 Postoperative complications and long-term survival

Major complications after surgery may be fatal. Nonfatal complications may still have a negative effect on HRQOL (60), length-of-stay (LoS) (61), and resource utilization (61). In addition, reports have indicated that even for patients initially surviving the double hit of surgery and a subsequent major complication, long-term survival will still be negatively affected (62;63). Khuri et al showed that patients experiencing a complication from surgery had a markedly reduced long-term survival even when those who died within 30 days of their complication were excluded from analysis (62). This has led to speculations whether major complications could have long-standing suppressive effects on a patient's immune system thereby rendering them more susceptible to cancer recurrence or another major disease (64). Their findings have been corroborated by several reports, but others again have failed to show this connection (65).

A distinct association between socioeconomic status and both postoperative morbidity and survival after cancer surgery has been shown (66-68). The association between socioeconomic status and survival cannot be fully explained by differences in either disease-stage or treatment, although these factors are thought to be significant (67). If these factors were the most important, one could hypothesize that the association would be weaker in societies with equal access to health care.

A validation of the possible relationship between non-fatal postoperative complications and survival is important, but factors like differences in socioeconomic status have to be properly accounted for. Adherence to enhanced recovery protocols (ERPs) has been proven to reduce postoperative morbidity (69). If postoperative morbidity is clearly linked to survival after cancer surgery, measures that have been proven to reduce morbidity such as ERPs (69) might even improve survival after cancer surgery.

3. OBJECTIVES

This thesis seeks to clarify the following issues concerning recovery and survival after upper abdominal surgery:

A. How do patients and dedicated professionals define recovery and which care elements are most crucial according to the same patients and professionals?
B. How do pretreatment body composition indices (relative amount of skeletal muscle and adipose tissue) correlate with outcome after upper abdominal surgery? How does *loss* of lean or adipose tissue during treatment correlate with outcome after upper abdominal surgery? How do body composition indices correlate with disease severity?
C. How does outcome after upper abdominal surgery correlate with new (body composition indices) compared to old (preoperative weight loss and serum-albumin) tools for risk/prognosis assessment?
D. How does survival after upper abdominal surgery correlate with pre- or postoperative self-reported health-related quality of life (HRQOL)? How does HRQOL correlate with other tools for risk/prognosis assessment?
E. Does postoperative morbidity (complications) correlate with long-term survival after upper abdominal surgery?

4. METHODS

4.1 Questionnaire survey (Paper I, II)

The questionnaire surveys were constructed within the ERAS (Enhanced Recovery After Surgery) Society collaboration.

In the first survey, dedicated professionals were asked to rate eight recovery targets and 13 care items on a Likert scale. The questionnaire was prepared for digital, web-based distribution by email and mailed to recipients between October and December 2012.

Two select groups of dedicated professionals were targeted. The first group was delegates to the first international ERAS congress in Cannes, France in October 2012. The second group consisted of participants selected through a PubMed search with the following search terms: (”enhanced recovery” OR ”critical pathway” OR ”fast track”) AND (surgery OR operation OR resection OR *ectomy) for the latest five years in English. The resulting list of papers was hand searched to yield only papers with a clear relevance to ERAS in abdominal surgery.

In the second survey, care providers and patients were approached with a questionnaire similar to the one used in the first survey. Patients received two questionnaires, preoperatively and 2-4 weeks after surgery. Care providers and patients were approached in three northern European university hospital centers; Tromsø (Norway), Edinburgh (United Kingdom) and Maastricht (the Netherlands), between November 2012 and November 2013.

4.2 Prospective cohort study (Paper III, IV)

From 2001 to 2006, 447 patients were included in a Norwegian multicenter randomized controlled trial (RCT), which investigated normal food at will after major upper surgery (70). The dataset from that study was now treated as a single, prospective cohort. Survival data from the Norwegian Population Registry were retrieved during April 2012, six years after the last patient was included in the original trial.

In addition to demographics and general clinical characteristics, the prospective database included specifically: patient-reported preoperative weight loss, preoperative serum-albumin, type of surgery, major postoperative complications and self-reported health-related quality of life (HRQOL).

Major complications, within eight weeks after surgery were defined a priori in the original trial (70). The operative procedures were listed in the original publication (70). Patients were divided into the following disease categories: Gastroesophageal cancer, pancreatic cancer, other cancer (mainly malignant liver tumors and liver metastasis) and non-cancer.

Preoperative weight loss was calculated from patients' usual pre-morbid weight as they reported it - with no time limit, and current weight as scaled preoperatively at trial enrolment. It was dichotomized into >5% or ≤5% weight loss. Preoperative serum-albumin was dichotomized into <35.0 g/l or ≥35.0 g/l.

Self-reported HRQOL was assessed preoperatively at trial enrollment and eight weeks after surgery. The validated Norwegian translation (71) of the generic health-related quality of life instrument: Short Form 36 (SF-36), Norwegian version 1.2, was utilized. While SF-36 is not a disease-specific instrument, it has been used and validated in a wide range of malignant and non-malignant diseases (55). SF-36 contains thirty-six questions that produce eight scales. These scales are; physical functioning, role limitation (caused by physical problems), bodily pain, general health, vitality, social functioning, role limitation (caused by emotional problems) and mental health. These scales were aggregated to produce a summary physical HRQOL score (Physical Component Summary, PCS) and a summary mental HRQOL score (Mental Component Summary, MCS) (72). These norm-based scores have a mean of 50 and a standard deviation of 10 in general adult populations (72). Reduced HRQOL were defined as summary scores lower than 50.

Digitally stored computer tomography (CT) images for initial routine diagnostics and staging were analyzed using Slice-O-Matic software V4.2 (Tomovision, Montreal-Canada) which permitted specific tissue demarcation using Houndsfield unit threshold of -29 to +150 for skeletal muscles (73), -150 to -50 for visceral adipose tissue (74), and -190 to -30 for subcutaneous adipose tissue (73). Cross-sectional areas (cm^2) were calculated for each tissue by summing tissue pixels and multiplying by the pixel surface area. A transverse CT image from the third lumbar vertebrae (L3) was assessed for each scan and tissue areas estimated (75). All CT images were analyzed by one single trained observer who was blinded to all clinical data. Cross-sectional area was normalized for stature (cm^2/m^2) and the following indices were calculated: L3 Skeletal muscle index (L3 SMI), L3 Visceral adipose tissue index (L3 VAT) and L3 Subcutaneous adipose tissue index (L3 SAT). CT images used for analysis were retrieved from routine examinations performed within three months preoperatively.

The cut-offs for L3 SMI suggested by Martin et al (50) were utilized: L3 SMI $<41\ cm^2/m^2$ for women, L3 SMI $<43\ cm^2/m^2$ for men with BMI $<25\ kg/m^2$ and L3 SMI $<53\ cm^2/m^2$ for men with BMI ≥25kg/m^2. We also used the cut-offs suggested first by Mourtzakis et al (47) and later in an international consensus paper (10). This cut-off corresponds to skeletal muscle mass two standard deviations from that of healthy young adults (39 cm^2/m^2 for women and 55 cm^2/m^2 for men) (10). Preoperative weight loss, serum-albumin and L3 SMI were analyzed both as dichotomous and continuous variables. L3 VAT and L3 SAT were analyzed only as continuous variables.

In the first paper, all patients with complete data sets for preoperative serum-albumin and weight loss were included in the analysis. A subgroup analysis was performed on patients with available preoperative CT images.

In the second paper, patients without any pre- or postoperative HRQOL data were excluded from further analysis.

4.3 Retrospective case series study (Paper V)

A complete cohort of all patients who underwent gastric resection for adenocarcinoma in the four-year period 2008-2011 in two Scandinavian referral centers (University hospital of Northern Norway, Tromsø, Norway and Karolinska University Hospital at Huddinge, Stockholm, Sweden) was retrospectively analyzed (n=137). Information on general characteristics, comorbidity, histopathological stage, chemotherapy treatment and -toxicity, postoperative complications and overall survival were retrieved from patient files.

The following investigations were performed separately:

- Tissue change during neoadjuvant chemotherapy (NAC): Patients with CT images of sufficient quality from the diagnostic/staging and the preoperative CT examination were included in this analysis.
- Preoperative body composition indices in relation to disease severity and clinical outcome: All patients with preoperative CT images of sufficient quality were included.
- Postoperative tissue change: Patients with CT images from the preoperative CT examination and furthermore one CT examination performed between one and twelve months postoperatively were included.

Body composition analysis based on computed tomography images are described in section 4.2. Total whole-body amount of lean tissue (FFM=fat-free mass) and fat tissue (FM=fat mass) were estimated from the following formulas (47):

FFM (kg) = 0.3 x L3 Skeletal muscle area (cm^2) + 6.06

FM (kg) = 0.042 x L3 Visceral and subcutaneous adipose tissue area (cm^2) + 11.2

Estimated total tissue (lean and fat tissue combined) was also calculated.

Dose Limiting Toxicity (DLT) was defined as chemotherapeutic side effects leading to chemotherapy dose reduction or abandonment (18). Complications were classified by the Accordion classification (76;77). Severe postoperative complications as a dichotomous outcome were defined as one or more Accordion III or higher complication (76;77).

4.4 Register study (Paper VI)

A database of surgical procedures, major postoperative complications and survival were extracted from the Norwegian Patient Registry (NPR). Data on educational level were extracted from Statistics Norway, the Norwegian central bureau of statistics.

We identified all resections of the esophagus, stomach and pancreas in the six-year period from January 1, 2008 to December 1, 2013. Data on overall survival until June 30, 2014 were retrieved. Operations and reoperations were identified from their Nomesco classification of Surgical Procedures (NCSP) code (2014).

Only cases with an appropriate cancer diagnosis (ICD-10: C15*, C16* and C25* respectively, where * denotes all sub-codes) applied within eight weeks from surgery were included. Emergency cases were excluded from to obtain a cohort of patients that were reasonably fit at index surgery.

Overall survival was defined as survival from index surgery. Major complications were defined as equivalent to Accordion score IV or higher (76;77), i.e. a re-operation in general anesthesia for a complication, and/or single- or multiple organ failure (76;77). We did not attempt to identify complications with lower severity score, as these complications would be difficult to extract from NPR data.

All stays in this database (containing an eligible index operation) were coupled with any subsequent stay at any Norwegian hospital with an admission date within 28 days of discharge from the index stay. Hospital stays (single or coupled) containing one or more major complications were identified. This was done by identification of one of the following procedure codes at index or subsequent stay: Reoperation for wound dehiscence (JWA00), for deep infection (JWC00/01), for deep hemorrhage (JWE00/01/02), for anastomotic dehiscence (JWF00/01) for other causes (JWW96/97/98) or if a tracheostomy was performed (GBB00/03). Also, a major complication was identified from the use of one of the following diagnoses during index or subsequent stays: Bleeding, hematoma or circulatory shock following a procedure (T81.0/T81.1).

Educational level was divided into higher and lower education. Higher education was defined as education beyond primary and lower secondary school. Surgical resections were stratified into esophageal-, gastric- and pancreatic resections.

5. METHODOLOGICAL DISCUSSION

Our conclusions are based on two questionnaire surveys, one prospective cohort study (a long-term follow-up of a randomized clinical trial, one retrospective case series study and one register study.

5.1 Questionnaire survey (Paper I, II)

The response rate in the first survey was 50%. This is within acceptable limits of surveys of this kind (78), although a higher response rate would have been preferable. The preoperative response rate was very high in the second survey (100%) with some missing data postoperatively (19% lost in follow-up). In both surveys, most of the recovery targets and care items received a high rating, indicating that the surveys lacked discriminatory power. The sample sizes were small in both surveys.

5.2 Prospective cohort study (Paper III, IV)

To our knowledge, this is the first study to observe both health-related quality of life (HRQOL) and body composition in multicenter prospective upper abdominal surgery cohort. Follow up was long, between six and twelve years. Data on survival was almost complete (98%).

Missing data

There were varying degrees of missing data on the different variables investigated. These varying degrees of missing data introduce possibilities for selection bias. Especially, there were many missing CT images from the first couple of years in the cohort. Furthermore, preoperative and postoperative HRQOL data were missing to a varying extent.

Heterogeneity in survival

Our cohort lacked data on disease stage and did not exclusively consist of cancer patients. Heterogeneity in survival was high. Still, survival analysis was stratified on the different disease categories and the effect of the variables investigated (weight loss, serum-albumin, body composition indices and HRQOL) was similar in the different disease categories.

5.3 Retrospective case series study (paper V)

A limitation of this study was its retrospective design. This type of design allows for errors when data is classified into different variables, in this case for example when whether patients experienced dose-limiting toxicity or postoperative complications. These outcome variables were retrospectively determined based on information from the patient's prospectively registered medical records.

Number of patients

Another limitation of this study was the relatively small number of patients included (n=137), especially the number of patients who received preoperative chemotherapy (n=58). There was little degree of missing data, but some patients lacked CT images of sufficient quality for body composition analyses. The relatively small number of patients analyzed may have contributed to the lack of association found between tissue loss and outcome.

Biases

Common biases of retrospective studies include selection bias and recall bias. Selection bias was limited in our study as our cohort consisted of all patients who underwent surgery for gastric adenocarcinoma in a four-year period in the two participating centers (University Hospitals of Tromsø, Norway and Huddinge - Stockholm, Sweden). This four – year interval were chosen due to the implementation of perioperative chemotherapy in the treatment of gastric adenocarcinoma in 2007 and to have sufficient observational time on all patients (three years). Recall bias was limited as information were prospectively recorded in the patient's medical journals.

5.4 Register study (paper VI)

The Norwegian patients registry (NPR) used for this study has some limitations, the varying quality of data in this registry and the number of variables missing in this registry. For this reason, the only variables collected were age, gender, type of operation, educational level (information gathered from Statistics Norway – the Norwegian central bureau of statistics), postoperative complications (assessed from the procedure and diagnosis codes) and overall survival.

Selection bias

This registry is national which limit the degree of potential selection bias, although there might be patients who were not included in our six – year cohort, due to limitations of our algorithm (described in section 4.4). Also, there might be postoperative complications not detected due to limitations of our algorithm. Although such selection and interpretation biases may exist, they are probably occurring randomly. A comparison of the yield from our refined search strings with hand searched patient files in a four-year cohort at our own hospital (150 patients) showed a 100% match in both number of resections and rate of major complications.

Number of patients

This study consisted of an unselected national cohort with almost 2000 patients, but the number of patients with higher educational level was relatively small (n=510). This might contribute to the lack of association between educational level and survival.

5.5 Association and causation (Paper III, IV, V and VI)

All of the observational studies in this thesis (paper III, IV, V and VI) allows for analyses of association and *not* causation. It would be very difficult to investigate whether abnormal serum-albumin, preoperative weight loss, low muscle mass, visceral obesity or decreased health-related quality of life *cause* decreased survival after upper abdominal surgery as these exposures are newer randomized. Can complications make patients more susceptible to cancer recurrence and therefore cause decreased longevity? This question can never be answered with a randomized human clinical trial. Sometimes causation may be evaluated through associations in observational studies (79) (it may sometimes be the only option).

6. OVERVIEW OF RESULTS

6.1 Rating of recovery targets and care items among dedicated professionals (Paper I)

The response rate was 50% of both congress participants and authors. Surgeons, anesthetists and nurses were represented. The recovery targets: *To be completely free of nausea*; *To be independently mobile* and *To be able to eat and drink as soon as possible* received the highest score irrespective of responder's profession or region of origin. Equally, the care items: *Optimizing fluid balance*; *Preoperative counseling* and *Promoting early and scheduled mobilization* received the highest score across all groups.

6.2 Rating of recovery targets and care items among caregivers and patients (Paper II)

One hundred nine patients and 57 care providers completed the preoperative survey. Overall, both patients and care providers rated the majority of items as important and supported ERAS principles. The recovery target *To be completely free of nausea* and the care item *Preoperative counseling* were rated the highest by both patients and care providers.

6.3 Risk factors, complications and survival (Paper III)

There were 447 patients included in the original trial. Complete information on preoperative weight loss and serum-albumin was available for 369 patients (82.5%). Preoperative CT images of sufficient quality were available in 157 of these patients (157/369=42.5%). Preoperative serum-albumin <35 g/l and weight loss >5% were independently associated with reduced survival. There was no association between any of the preoperative body composition indices and reduced survival. Major postoperative complications were independently associated with reduced survival but only as long as patients who died within 90 days were included in the analysis.

6.4 Health-related quality of life (HRQOL) and survival (paper IV)

A majority of the patients experienced improved mental HRQOL and, to a lesser extent, deteriorated physical HRQOL following surgery. There was a significant association between preoperative weight loss and reduced physical HRQOL. No association between low muscle mass and HRQOL was observed. Reduced physical HRQOL both pre- and postoperatively, and reduced postoperative mental HRQOL was significantly associated with impaired survival. The association between HRQOL and survival was particularly strong for postoperative physical HRQOL.

6.5 Body composition analyses and outcome in patients with resectable gastric adenocarcinoma (Paper V)

Of the 137 patients who underwent gastric resection in the period, 70 patients (51.1%) patients died within three years. Neoadjuvant chemotherapy was given to 58 (42.3%) patients and forty (29.2%) patients suffered severe postoperative complications. There was a significant reduction in patients' lean tissue during neoadjuvant chemotherapy (p=0.001), but no association between such loss and any recorded outcome including dose-limiting toxicity. Older age and female gender, but not advanced histopathological stage, was associated with lower preoperative skeletal muscle tissue index. Poorer survival was observed in patients with preoperative skeletal muscle tissue index within the lowermost quartile (HR=2.08, 95% CI=1.21-3.57, p=0.008) such association was also observed independently of disease stage (HR=1.91, 95% CI 1.11-3.28, p=0.019). There was no association between low preoperative muscularity and impaired survival when any of the cut-offs established in other studies (47;50) were investigated. A significant loss of both lean (p<0.001) and fat tissue (p<0.001) was observed postoperatively.

6.6 Association between suffering major postoperative complications and decreased survival after major upper abdominal surgery (Paper VI)

There were 1965 esophageal-, gastric- or pancreatic resections performed for cancer in Norway during 2008-2013. A total of 248 patients (12.6%) suffered major postoperative complications. Complications were associated with increased both early mortality (90 days mortality: OR=4.25, 95% CI=2.78-6.51), and overall survival when patients suffering early mortality were excluded (HR=1.23, 95% CI=1.01-1.23). Lower educational level was associated with increased rate of major postoperative complications (OR=1.41, 95% CI 1.02-1.95). Educational level was not associated with survival and did not affect the association between complications and survival.

7. GENERAL DISCUSSION

Avoidance of postoperative morbidity, fast recovery, improved quality of life and ultimately improved survival are essential goals in upper abdominal surgery. The first three goals are important in itself but the achievement of these goals may also *lead* to improved long-term survival, even in patients with aggressive upper abdominal malignant disease.

Success in this setting is challenging, as upper abdominal surgery often involves complex procedures associated with postoperative morbidity and functional impairment. Patients are often weakened by their disease preoperatively and they may suffer from both cachexia and low muscularity. Therefore, both optimal operative *and* perioperative treatment are required. Optimal perioperative treatment involves evidence-based and individualized care based on proper risk assessment. Such care demands high-quality research, which again requires proper definitions of recovery and validated, objective and widely accepted risk-stratification tools.

7.1 Defining recovery and the most crucial perioperative care item.

Our research has demonstrated a striking uniformity in the way international expertise and patients scored the relative importance of recovery targets. Functional recovery, as intolerance of food without nausea and regained mobility, was considered the most important target for recovery and might be used as one definition of recovery in future research and audits. Preoperative counseling seems to be the most important perioperative care item when combining the evaluation of both dedicated professionals and patients. This item is intuitively very important and has little or no side-effects, but the strength of evidence behind it is sparse (80-83). This might show that optimal care cannot be based randomized controlled trials alone, good old “common-sense” is still important in the era of evidence-based medicine and Cochrane reviews.

7.2 Risk assessment

Traditional risk assessment tools

There are several well-known global indicators of both increased risk of postoperative morbidity and impaired survival. Abnormal serum-albumin and preoperative self-reported weight loss might be the most widely accepted indicators in digestive surgery and their importance has been recognized for several decades (32-34). These indicators are inexpensive to utilize and they are easily available. However, abnormal serum-albumin can be hard to interpret as it is influenced by many factors. Assessment of preoperative weight loss relies on patients’ recollection of pre-morbid weight, which might be inaccurate.

Despite these weaknesses, our research has again confirmed the importance of assessing preoperative serum-albumin and weight loss, as these indicators again proved to be globally associated with impaired survival after upper abdominal surgery.

Novel risk assessment tools

Patients with upper abdominal malignancies often suffer from cachexia and sarcopenia (17;36;84), which again is associated with postoperative morbidity and poor prognosis (19;22).

Cachexia is defined as “A multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment” (10).

Sarcopenia has no universally accepted definition, and the term is both used when referring to low muscularity (measured at one time-spot, for example preoperatively) and loss of skeletal muscle tissue (85;86).

Body composition analyses (evaluating patients’ relative amount of skeletal muscle and adipose tissue) have existed for several decades. Such analyses have also been used to investigate changes in the same tissue. Body composition analyses have been utilized in many different fields of medicine including physiology, geriatric medicine, cardiology, respiratory medicine, oncology and surgery. Several methods for body composition analysis has been utilized including in vivo neutron activation analysis (IVNAA) (87), whole body dual energy x-ray densitometry (DXA) (47) and bioelectrical impedance analysis (BIA) (47). The most recent method is the measurement of specific tissue area on computed tomography (CT) or magnetic resonance (MR) images (47). This measurement is based on tissue demarcation and both whole body tissue estimates and tissue indices relative to patients’ stature can be created (47). Body composition analysis based on CT images are easily available in upper abdominal surgery as almost every patient will be subjected to one or several CT examinations during their course of treatment (47).

Our research has demonstrated that tissue loss during perioperative treatment for gastric adenocarcinoma can be easily quantified. Patients seem to experience a substantial loss of tissue, but such loss is yet to be linked to outcome. Body composition indices do not seem to represent global indicators of postoperative morbidity and impaired survival. However, in gastric adenocarcinoma, patients with the lowermost preoperative muscularity seem to have the poorest prognosis. This association seems to be independent of disease stage.

Body composition analysis might be important tools of risk assessment and research, and there might be areas within digestive surgery in which these analyses has an especially important role (88), examples may include predicting pulmonary complications after esophagectomies (42) and pancreatic fistulas after pancreaticoduodenectomies (43;44). However, the cut-offs and clinical relevance have to be investigated and validated disease-specifically. Global cut-offs do not seem to exist.

7.3 Postoperative morbidity, health-related quality of life and survival

Avoidance of complications is of the utmost importance as complications are associated with reduced health-related quality of life (60) and increased resource utilization (89). Complications may also preclude or delay adjuvant chemotherapy (90).

Reports have indicated that complications may be associated with decreased long-term survival, also when patients with early mortality are excluded from analysis (62;65;91;92). In this setting, it has been suggested that major complications could have long-standing suppressive effects on a patient's immune system and thereby render them more susceptible to cancer recurrence (62;64;91;92). The association between postoperative complications and long-term survival has not been consistently confirmed in upper abdominal cancer surgery (65), where both major complications and early recurrence is common (15;93).

Our research has demonstrated that major postoperative complications are associated with both early mortality and decreased long-term survival after gastro-esophageal and pancreatic cancer surgery in a national perspective. Systematic quality improvement to avoid complications may improve the poor prognosis associated these cancers.

Our research has also demonstrated an association between postoperative complications and physical health-related quality of life (HRQOL). Furthermore, a distinct association between postoperative HRQOL and long-term survival was observed. These findings emphasize the importance of avoiding postoperative complications. Identifying patients with reduced postoperative HRQOL and paying more attention to their functional impairments may improve long-term HRQOL and *even* survival with little or no side-effects.

8. MAIN CONCLUSIONS

Recovery of mobility and GI function are the most important target of convalescence after surgery. The traditional global indicators of poor prognosis after surgery, preoperative weight loss and abnormal serum-albumin, are still valid today. There is a close correlation between functional impairment and prognosis after major upper abdominal surgery. Tissue loss during surgical and oncological treatment for upper abdominal cancer can be evaluated through routine CT examinations. Preoperative low muscularity is independently associated with poor prognosis after resection for gastric adenocarcinoma. However, preoperative body composition indices do not seem to be global indicators of poor prognosis as importance and cut-offs seem to vary with different diseases. Postoperative morbidity is associated with poor long-term survival after major upper abdominal cancer surgery.

9. IDEAS FOR FURTHER RESEARCH IN UPPER ABDOMINAL SURGERY

- Future research on convalescence after surgery might replace “length of stay” with “time to functional recovery” (recovery of GI function and mobility) as an outcome.
- Clinically relevant and disease-specific cut-offs for skeletal muscle and visceral adipose tissue indices in surgical oncology should be developed and validated. Associations with disease-stage should be further explored.
- Treatment toxicity and effect (chemotherapeutics and antibiotics) in relation to the amount of skeletal and adipose tissue should be further explored.
- Tissue loss preoperatively (during neoadjuvant chemotherapy) and postoperatively in surgical oncology should be further explored together with clinical relevance of such loss (associations with morbidity and survival).
- Tissue change (evaluated through body composition analyses) could be an outcome measure in future research on prehabilitation and rehabilitation.
- Survival benefit of assessing postoperative HRQOL and functional recovery (and intervening on problems identified) should be explored.
- Survival benefit (long-term survival) of implementing programs to reduce postoperative complications should be explored.

REFERENCES

1. MOORE FD. Getting well: the biology of surgical convalescence. Ann.N.Y.Acad.Sci. 1958;73(2)387-400.

2. Malietzis G, Aziz O, Bagnall NM, et al. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: A systematic review. Eur.J.Surg.Oncol. 2015;41(2)186-196.

3. Aahlin EK, von MM, Dejong CH, et al. Functional recovery is considered the most important target: a survey of dedicated professionals. Perioper.Med.(Lond). 2014;3:5. doi: 10.1186/2047-0525-3-5. eCollection;%2014.5-3.

4. Hughes M, Coolsen MM, Aahlin EK, et al. Attitudes of patients and care providers to enhanced recovery after surgery programs after major abdominal surgery. J.Surg.Res. 2015;193(1)102-110.

5. Aahlin EK, Trano G, Johns N, et al. Risk factors, complications and survival after upper abdominal surgery: a prospective cohort study. BMC.Surg. 2015;15:83. doi: 10.1186/s12893-015-0069-2.83-0069.

6. Aahlin EK, Trano G, Johns N, et al. Health-Related Quality of Life, Cachexia and Overall Survival After Major Upper Abdominal Surgery: A Prospective Cohort Study. Scand.J.Surg. 2016.

7. Aahlin EK, Olsen F, Uleberg B, et al. Major postoperative complications are associated with impaired long-term survival after gastro-esophageal and pancreatic cancer surgery: a complete national cohort study. BMC.Surg. 2016;16(1)32.

8. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann.Surg. 2008;248(2)189-198.

9. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN J.Parenter.Enteral Nutr. 2014;38(8)940-953.

10. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5)489-495.

11. Fearon K, Evans WJ, Anker SD. Myopenia-a new universal term for muscle wasting. J.Cachexia.Sarcopenia.Muscle. 2011;2(1)1-3.

12. Malietzis G, Currie AC, Athanasiou T, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. Br.J.Surg. 2016;103(5)572-580.

13. Li QG, Li P, Tang D, et al. Impact of postoperative complications on long-term survival after radical resection for gastric cancer. World J.Gastroenterol. 2013;19(25)4060-4065.

14. Velanovich V. The association of quality-of-life measures with malignancy and survival in patients with pancreatic pathology. Pancreas. 2011;40(7)1063-1069.

15. Bringeland EA, Wasmuth HH, Johnsen G, et al. Outcomes among patients treated for gastric adenocarcinoma during the last decade. J.Surg.Oncol. 2013;107(7)752-757.

16. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N.Engl.J.Med. 2014;371(11)1039-1049.

17. Tan BH, Birdsell LA, Martin L, et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin.Cancer Res. 2009;15(22)6973-6979.

18. Tan BH, Brammer K, Randhawa N, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. Eur.J.Surg.Oncol. 2014;(14)10.

19. Joglekar S, Nau PN, Mezhir JJ. The impact of sarcopenia on survival and complications in surgical oncology: A review of the current literature. J.Surg.Oncol. 2015;112(5)503-509.

20. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7)629-635.

21. Reisinger KW, van Vugt JL, Tegels JJ, et al. Functional Compromise Reflected by Sarcopenia, Frailty, and Nutritional Depletion Predicts Adverse Postoperative Outcome After Colorectal Cancer Surgery. Ann.Surg. 2014;%19.

22. Levolger S, van Vugt JL, de Bruin RW, et al. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. Br.J.Surg. 2015;102(12)1448-1458.

23. Ishizawa T, Gumbs AA, Kokudo N, et al. Laparoscopic segmentectomy of the liver: from segment I to VIII. Ann.Surg. 2012;256(6)959-964.

24. Tzeng CW, Fleming JB, Lee JE, et al. Yield of clinical and radiographic surveillance in patients with resected pancreatic adenocarcinoma following multimodal therapy. HPB (Oxford). 2012;14(6)365-372.

25. Viste A, Rygh AB, Soreide O. Cancer of the stomach--is a follow-up program of any importance for the patient? Clin.Oncol. 1984;10(4)325-332.

26. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N.Engl.J.Med. 2006;355(1)11-20.

27. Holmebakk T, Frykholm G, Viste A. Introducing national guidelines on perioperative chemotherapy for gastric cancer in Norway: a retrospective audit. Eur.J.Surg.Oncol. 2010;36(7)610-616.

28. Bringeland EA, Wasmuth HH, Fougner R, et al. Impact of perioperative chemotherapy on oncological outcomes after gastric cancer surgery. Br.J.Surg. 2014;101(13)1712-1720.

29. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am.J.Surg. 2002;183(6)630-641.

30. Neville A, Lee L, Antonescu I, et al. Systematic review of outcomes used to evaluate enhanced recovery after surgery. Br.J.Surg. 2014;101(3)159-171.

31. Studley HO. Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. 1936. Nutr.Hosp. 2001;16(4)141-143.

32. Daley J, Khuri SF, Henderson W, et al. Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: results of

the National Veterans Affairs Surgical Risk Study. J.Am.Coll.Surg. 1997;185(4)328-340.

33. Khuri SF, Daley J, Henderson W, et al. Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. J.Am.Coll.Surg. 1997;185(4)315-327.

34. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am.J.Med. 1980;69(4)491-497.

35. Cooper AB, Slack R, Fogelman D, et al. Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. Ann.Surg.Oncol. 2014.

36. Awad S, Tan BH, Cui H, et al. Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. Clin.Nutr. 2012;31(1)74-77.

37. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin.Cancer Res. 2009;15(8)2920-2926.

38. Del FE, Parsons H, Warneke CL, et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. Oncologist. 2012;17(10)1240-1245.

39. Itoh S, Shirabe K, Matsumoto Y, et al. Effect of Body Composition on Outcomes after Hepatic Resection for Hepatocellular Carcinoma. Ann.Surg.Oncol. 2014.

40. Sabel MS, Terjimanian M, Conlon AS, et al. Analytic morphometric assessment of patients undergoing colectomy for colon cancer. J.Surg.Oncol. 2013;108(3)169-175.

41. Miller BS, Ignatoski KM, Daignault S, et al. Worsening central sarcopenia and increasing intra-abdominal fat correlate with decreased survival in patients with adrenocortical carcinoma. World J.Surg. 2012;36(7)1509-1516.

42. Nishigori T, Okabe H, Tanaka E, et al. Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer. J.Surg.Oncol. 2016;10.

43. Pecorelli N, Carrara G, De CF, et al. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. Br.J.Surg. 2016;103(4)434-442.

44. Kirihara Y, Takahashi N, Hashimoto Y, et al. Prediction of pancreatic anastomotic failure after pancreatoduodenectomy: the use of preoperative, quantitative computed tomography to measure remnant pancreatic volume and body composition. Ann.Surg. 2013;257(3)512-519.

45. Yamaoka Y, Fujitani K, Tsujinaka T, et al. Skeletal muscle loss after total gastrectomy, exacerbated by adjuvant chemotherapy. Gastric.Cancer. 2015;18(2)382-389.

46. Malietzis G, Currie AC, Johns N, et al. Skeletal Muscle Changes After Elective Colorectal Cancer Resection: A Longitudinal Study. Ann.Surg.Oncol. 2016.

47. Mourtzakis M, Prado CM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl.Physiol Nutr.Metab. 2008;33(5)997-1006.

48. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. J.Am.Coll.Surg. 2010;211(2)271-278.

49. Amini N, Spolverato G, Gupta R, et al. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. J.Gastrointest.Surg. 2015;19(9)1593-1602.

50. Martin L, Birdsell L, MacDonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J.Clin.Oncol. 2013;31(12)1539-1547.

51. van Vledder MG, Levolger S, Ayez N, et al. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br.J.Surg. 2012;99(4)550-557.

52. Parekh NR, Steiger E. Percentage of weight loss as a predictor of surgical risk: from the time of Hiram Studley to today. Nutr.Clin.Pract. 2004;19(5)471-476.

53. Quinten C, Coens C, Mauer M, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. Lancet Oncol. 2009;10(9)865-871.

54. Lis CG, Gupta D, Lammersfeld CA, et al. Role of nutritional status in predicting quality of life outcomes in cancer--a systematic review of the epidemiological literature. Nutr.J. 2012;11:27. doi: 10.1186/1475-2891-11-27.27-11.

55. Frendl DM, Ware JE, Jr. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. Med.Care. 2014;52(5)439-445.

56. Kuchler T, Bestmann B, Rappat S, et al. Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial. J.Clin.Oncol. 2007;25(19)2702-2708.

57. Thoresen L, Frykholm G, Lydersen S, et al. The association of nutritional assessment criteria with health-related quality of life in patients with advanced colorectal carcinoma. Eur.J.Cancer Care (Engl.). 2012;21(4)505-516.

58. Thompson CA, Charlson ME, Schenkein E, et al. Surveillance CT scans are a source of anxiety and fear of recurrence in long-term lymphoma survivors. Ann.Oncol. 2010;21(11)2262-2266.

59. Kiebert GM, Welvaart K, Kievit J. Psychological effects of routine follow up on cancer patients after surgery. Eur.J.Surg. 1993;159(11-12)601-607.

60. Brown SR, Mathew R, Keding A, et al. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann.Surg. 2014;259(5)916-923.

61. Knechtle WS, Perez SD, Medbery RL, et al. The Association Between Hospital Finances and Complications After Complex Abdominal Surgery: Deficiencies in the

Current Health Care Reimbursement System and Implications for the Future. Ann.Surg. 2014.

62. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann.Surg. 2005;242(3)326-341.

63. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, et al. Anastomotic Leak Increases Distant Recurrence and Long-Term Mortality After Curative Resection for Colonic Cancer: A Nationwide Cohort Study. Ann.Surg. 2013.

64. Mavros MN, de JM, Dogeas E, et al. Impact of complications on long-term survival after resection of colorectal liver metastases. Br.J.Surg. 2013;100(5)711-718.

65. Pucher PH, Aggarwal R, Qurashi M, et al. Meta-analysis of the effect of postoperative in-hospital morbidity on long-term patient survival. Br.J.Surg. 2014;101(12)1499-1508.

66. Dik VK, Aarts MJ, Van Grevenstein WM, et al. Association between socioeconomic status, surgical treatment and mortality in patients with colorectal cancer. Br.J.Surg. 2014;101(9)1173-1182.

67. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Ann.Oncol. 2006;17(1)5-19.

68. Frederiksen BL, Osler M, Harling H, et al. The impact of socioeconomic factors on 30-day mortality following elective colorectal cancer surgery: a nationwide study. Eur.J.Cancer. 2009;45(7)1248-1256.

69. Gustafsson UO, Hausel J, Thorell A, et al. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch.Surg. 2011;146(5)571-577.

70. Lassen K, Kjaeve J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann.Surg. 2008;247(5)721-729.

71. Loge JH, Kaasa S, Hjermstad MJ, et al. Translation and performance of the Norwegian SF-36 Health Survey in patients with rheumatoid arthritis. I. Data quality, scaling assumptions, reliability, and construct validity. J.Clin.Epidemiol. 1998;51(11)1069-1076.

72. Ware JE, Kosinski E, Keller SD. SF-36:Physical and Mental Component Summary Scales: A user's Manual, Boston, MA, The Health Institute, New England Medical Centre, 1994.

73. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, et al. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J.Appl.Physiol (1985.). 1998;85(1)115-122.

74. Miller KD, Jones E, Yanovski JA, et al. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet. 1998;351(9106)871-875.

75. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J.Appl.Physiol (1985.). 2004;97(6)2333-2338.

76. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann.Surg. 2009;250(2)177-186.

77. Porembka MR, Hall BL, Hirbe M, et al. Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the american college of surgeons national surgical quality improvement program. J.Am.Coll.Surg. 2010;210(3)286-298.

78. Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. J.Clin.Epidemiol. 1997;50(10)1129-1136.

79. HILL AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc.R.Soc.Med. 1965;58:295-300.295-300.

80. Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. World J.Surg. 2013;37(2)240-258.

81. Nygren J, Thacker J, Carli F, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. World J.Surg. 2013;37(2)285-305.

82. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. World J.Surg. 2013;37(2)259-284.

83. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Br.J.Surg. 2014;101(10)1209-1229.

84. Tan BH, Brammer K, Randhawa N, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. Eur.J.Surg.Oncol. 2015;41(3)333-338.

85. Cesari M, Fielding RA, Pahor M, et al. Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. J.Cachexia.Sarcopenia.Muscle. 2012;3(3)181-190.

86. von HS, Morley JE, Anker SD. From muscle wasting to sarcopenia and myopenia: update 2012. J.Cachexia.Sarcopenia.Muscle. 2012;3(4)213-217.

87. Windsor JA, Hill GL. Weight loss with physiologic impairment. A basic indicator of surgical risk. Ann.Surg. 1988;207(3)290-296.

88. Braga M, Sandrucci S. Perioperative nutrition in cancer patients. Eur.J.Surg.Oncol. 2016.

89. Knechtle WS, Perez SD, Medbery RL, et al. The Association Between Hospital Finances and Complications After Complex Abdominal Surgery: Deficiencies in the Current Health Care Reimbursement System and Implications for the Future. Ann.Surg. 2015;262(2)273-279.

90. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, et al. Anastomotic Leak Increases Distant Recurrence and Long-Term Mortality After Curative Resection for Colonic Cancer: A Nationwide Cohort Study. Ann.Surg. 2014;259(5)930-938.

91. Tokunaga M, Tanizawa Y, Bando E, et al. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. Ann.Surg.Oncol. 2013;20(5)1575-1583.

92. Artinyan A, Orcutt ST, Anaya DA, et al. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. Ann.Surg. 2015;261(3)497-505.

93. Rustgi AK, El-Serag HB. Esophageal carcinoma. N.Engl.J.Med. 2014;371(26)2499-2509.