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Minimally Invasive Esophageal Resection for Cancer

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Summary and conclusions

This thesis focusses on several aspects of minimally invasive esophageal resection for cancer.

In **chapter 2** and **chapter 3** we reviewed the literature on minimally invasive esophageal resection. Where chapter two focuses on minimally invasive esophageal resection for malignancies of the distal esophagus, chapter three focuses on the thoracoscopic approach for esophageal resection. Both reviews highlight the indications for the different minimally invasive approaches as well as the detailed surgical techniques of the different operations.

In **chapter 4** we describe the short and long term results of the first 50 laparoscopic transhiatal esophageal resections for malignancies of the distal esophagus. We prospectively collected data on pre-operative characteristics, intra-operative results, tumor characteristics, morbidity, mortality and oncological results on short- and long-term. All patients were operated upon between January 2001 and January 2005. The median operation time was 300 minutes, median blood loss was 500 ml. Median postoperative ICU stay was one day and the median hospital stay was 13 days. Median follow-up was 35 months, median overall survival was 34 months. Kaplan-Meier analysis 36 months showed an overall survival of 36%. Median disease free survival was 30 months. Postoperative complications occurred in 21 patients (42%). Pulmonary and cardiac complications were observed in 9 (18%) and 3 (6%) patients respectively. Re-operation rate was (4%). No mortality was recorded. Conversions took place in 9 (18%) patients. We concluded that laparoscopic transhiatal esophagectomy for tumors of the distal esophagus is a feasible and safe procedure in experienced hands. A randomized study would further clarify the role of a laparoscopic approach for distal esophageal cancer

In **chapter 5** we compared the result as described in chapter 4 with a historical

cohort of 50 open transhiatal resections between January 1998 and December 2000. Laparoscopic esophageal resection was associated with less blood loss (500 vs 900 ml, $p < 0.001$), shorter intensive care unit stay (1.0 vs 3.0 days, $p < 0.001$), and shorter hospital stay (13 vs 16 days, $p < 0.001$). Conversion was necessary in 9 patients (18%). There were no differences in mortality and operating time. There were less pulmonary and cardiac complications although not significant ($p = 0.130$). Kaplan-Meier analysis at 12 months showed an overall survival of 89.6% (95% confidence interval: 81.0-98.2) for the laparoscopic group and 72% (95% confidence interval: 59.5-84.4) for the open group ($p = 0.476$). Kaplan-Meier analysis at 36 months showed an overall survival of 36% (95% confidential interval: 16.1-55.9) for the laparoscopic group and 38.3% (95% confidential interval: 24.4-52.2) for the open group. Mean disease free survival at 12 and 36 months was 74.2% respectively 26.6% (95% confidential interval: 61.5-86.8 respectively 22.9-58.0) for the laparoscopic group versus 65.9% respectively 33.7% (95% confidential interval: 52.8-79.1 respectively 29.2-64.0) for the open group.

In conclusion we stated that laparoscopic transhiatal esophagus resection in experienced hands is a safe procedure with important advantages over the open procedure. Moreover, there are no differences in overall and disease free survival between both groups.

Chapter 6 issues the immunological consequences of laparoscopic versus open transhiatal resection for malignancies of the distal esophagus and gastroesophageal junction. seventeen patients undergoing laparoscopic or open surgery were included in the study. The postoperative inflammatory response was assessed by measuring the WBC, CRP, IL-6, sTNFr I and II, IL-8 and elastase. Post-operative immune function was assessed by measuring monocyte HLA-DR expression. LBP and BPI were measured to evaluate bacterial translocation. We observed IL-6 and increasing significantly more in the patients who received open surgery, as compared to the laparoscopic

group. Both LBP and BPI increased predominantly in the laparoscopic group, as compared to the group who received open surgery. No difference was found in HLA-DR expression between the two groups. We concluded that although both laparoscopic and conventional esophageal resection results in an activation of the inflammatory response, this study suggests that this response could be less after the laparoscopic approach. However, in the laparoscopic group higher LBP and BPI levels were seen, suggesting a increased endotoxemia. We postulated that the persistently elevated abdominal pressure results in a loss of mucosal barrier function resulting in bacterial translocation. The cellular acidification of the cells of the peritoneum induced by CO₂ insufflation, however, blunts the expected inflammatory response.

In **chapter 7** We studied the influence of circumferential resection margin (CRM) involvement on survival in patients with malignancies of the distal esophagus and gastro-esophageal junction. In this study 110 consecutive patients undergoing a laparoscopic or an open transhiatal esophagectomy for malignancy of the distal 5 centimetres of the esophagus, or a Siewert I gastro-esophageal junction tumor were analysed retrospectively. Only patients with potentially resectable tumors were included. CRM status was defined as clear or involved (microscopic tumor within 1 mm of the resection margin). Statistical analysis was done by means of univariate and multivariate analysis using the Kaplan-Meier method and Cox proportional hazard model.

60 patients underwent open and 50 patients underwent laparoscopic transhiatal esophagectomy. There were 6 (5%) T₁, 18 (16%) T₂ and 86 (89%) T₃ tumors. CRM was clear in 68 (62%) patients and involved in 42 (38%) patients. Median survival in these groups was 50 vs. 20 months ($p=0.000$). Since CRM involvement was only seen in T₃ tumors this group was analysed in detail. Median survival in the T₃CRM- and T₃CRM+ group was 33 vs. 19 months ($p=0.004$). For T₃No tumors median survival in CRM- and CRM+ was 40 and 22 months respectively ($p=0.036$). Median survival for T₃N₁

tumors in CRM- and CRM+ was 22 and 13 months respectively ($p=0.049$). In conclusion involvement of the circumferential resection margin was found to be an independent prognostic factor on survival in our study. It predicts a poor prognosis in patients with potentially resectable malignancies of the distal 5 centimetres of the esophagus and Siewert I adenocarcinomas of the gastro esophageal junction.

We describe our standardized thoracoscopic esophagectomy in prone decubitus position followed by laparoscopy and present the early results in **chapter 8**. In this retrospective analysis we describe the operative technique of ten patients with esophageal cancer of the mid esophagus, not included in the national CROSS trial (neoadjuvant chemo-radiotherapy followed by conventional surgery versus surgery alone) underwent thoracoscopic esophagectomy in prone decubitus position followed by laparoscopy between March 2007 and July 2008. There were eight male and two female patients, mean age 67 years (48-80 years). Three tumors were squamous cell carcinomas and seven were adenocarcinomas. One conversion to thoracotomy was necessary. Mean operative time of the thoracoscopic approach was 130 minutes, being the total time of 290 minutes (range 240 to 460 minutes). Blood loss was 220 cc (range 250 to 400 cc). Mean ICU stay was 1 day (range 1 to 37 days) and mean hospital stay was 13 days (range 12 to 78 days). There was no perioperative mortality. Pathological examination showed a R0 resection in nine patients with a complete response after chemoradiation in one patient. Median number harvested lymphnodes was 21 (range 15 to 33). Postoperative complications were seen in three patients. one of them suffered from pulmonary complications together with anastomotic complications requiring reoperation in one patient. On chylothorax was seen.

In conclusion thoracoscopic approach of the esophageal cancer in the prone position is a promising relative new approach for esophageal resection. The advantage of a single lumen intubation and the 'only' partial collapse of the

lung during the resection may reduce the postoperative pulmonary complications compared with other approaches in which total collapse of the lung is necessary.

A systematic approach of postoperative gastric tube complications after esophageal resection is discussed in **chapter 9**. We evaluated the value and safety of early endoscopy as tool for inspecting the viability of the gastric conduit. Furthermore we evaluated the outcome of placement of a covered stent in case of anastomotic leakage. A retrospective analysis of 47 consecutive patients that underwent esophageal resection for cancer was done. 11 patients underwent upper endoscopy as well as CT scanning of thorax and abdomen because of a suspected anastomotic leakage. According to the findings on ct scanning and upper endoscopy patients were treated in a tailor made way. We concluded that it is safe to perform an early endoscopy and that placement of a covered stent is a safe and efficient way for the treatment of some types of anastomotic leakage. Furthermore we developed a flow chart with diagnostic and therapeutic options in case of clinical deterioration.

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And finally in **chapter 10** in an attempt to improve survival we performed this phase II study with chemoimmunotherapy. Patients with potentially resectable esophageal carcinoma, stages T₂N₁M₀ through T₃N₁M_{1a}, were treated with Gemcitabine (1250mg/m²; day 1 and 8) followed by Cisplatin (80mg/m²; day 1) and GM-CSF (300µg/day; day 9-19). Patients received one cycle every 3 weeks, up to a maximum of 6 cycles, after which the option of an esophagectomy was reviewed. Toxicity, tumor response and survival were analyzed.

Thirty-eight patients with a median age of 59,5 years were included. Twenty-nine patients (76%) completed the total of 6 chemotherapy cycles. Hematological toxicity was manageable with a grade 3 or 4 anemia, thrombocytopenia and leucopenia occurring in 21%, 55% and 18% of patients, respectively.

Neutropenic fever was observed in 5 patients (13%) and was manageable with intravenous antibiotics. No chemotherapy-related deaths occurred. One patient (3%) had a complete remission, fifteen patients (39%) had down staging in T and/or N stage, 8 patients (21%) had stable disease and 14 patients (37%) had progressive disease. Median overall survival was 24 months (95% confidence interval: 19-29) with a 2 year survival of 45% (95% confidence interval: 29-61). Six patients are alive and disease free at 72, 57, 44, 43, 43 and 38 months of follow-up. Although this is a small phase II study, we conclude that the overall survival with cisplatin-gemcitabine plus GM-CSF seems acceptable for the advanced disease included in this study, amid significant though manageable toxicity. Larger randomized studies are needed to compare this therapy to other chemotherapy schedules.