Pretherapeutic evaluation of patients with upper gastrointestinal tract cancer using endoscopic and laparoscopic ultrasonography

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This thesis is based on the following publications:

I. Mortensen MB. Endoscopic Ultrasonography (EUS) in malignant tumors of the upper gastrointestinal tract. PhD Thesis, Odense University: Odense 1996.
II. Mortensen MB, Ainsworth AP, Langkilde LK, Scheel-Hincke JD, Pless T, Hovendal C. Cost-effectiveness of different diagnostic strategies in patients with nonresectable upper gastrointestinal tract malignancies. Surg Endosc. 2000;14(3):278-81.
III. Mortensen MB, Pless T, Durup J, Ainsworth AP, Plagborg GJ, Hovendal C. Clinical impact of endoscopic ultrasound-guided fine needle aspiration biopsy in patients with upper gastrointestinal tract malignancies. A prospective study. Endoscopy 2001;33(6):478-83.
IV. Mortensen MB, Durup J, Pless T, Plagborg GJ, Ainsworth AP, Nielsen HO, Hovendal C. Initial experience with new dedicated needles for laparoscopic ultrasound-guided fine-needle aspiration and histological biopsies. Endoscopy. 2001;33(7):585-9
V. Mortensen MB, Fristrup C, Holm FS, Pless T, Durup J, Ainsworth AP, Nielsen HO, Hovendal C. Prospective evaluation of patient tolerability, satisfaction with patient information, and complications in endoscopic ultrasonography. Endoscopy. 2005;37(2):146-53.
VI. Mortensen MB, Fristrup CW, Ainsworth AP, Pless T, Nielsen HO, Hovendal C. Combined preoperative endoscopic and laparoscopic ultrasonography for prediction of R0 resection in upper gastrointestinal tract cancer. Br J Surg. 2006;93(6):720-5.
VII. Mortensen MB, Edwin B, Hunerbein M, Liedman B, Nielsen HO, Hovendal C. Impact of endoscopic ultrasonography (EUS) on surgical decision-making in upper gastrointestinal tract cancer: An international multicenter study. Surg Endosc. 2007;21(3):431-8.
VIII. Mortensen MB, Fristrup CW, Ainsworth AP, Pless T, Larsen MH, Nielsen HO, Hovendal C. Laparoscopic ultrasound-guided biopsy in upper gastrointestinal tract cancer patients. Surg Endosc 2009;23(12):2738-42.
IX. Mortensen MB, Fristrup CW, Ainsworth A, Nielsen HO, Pless T, Hovendal C. Combined pretherapeutic endoscopic and laparoscopic ultrasonography may predict survival of patients with upper gastrointestinal tract cancer. Surg Endosc 2011;25(3):804-12.

1. INTRODUCTION

Upper gastrointestinal tract cancer (UGIC) covers carcinoma of the esophagus, stomach and pancreas and approximately 2000 new cases of UGIC are diagnosed in Denmark each year. The different types of UGIC display varying survival rates and less than half of the referred patients will go to intended curative surgical resection. As a consequence of that, only a minor fraction of patients are alive and disease free after five years. Efforts to improve overall survival include early detection, extended surgical resections and neo-adjuvant/adjuvant therapy, but none of these factors have made substantial progress over the last decades. Careful patient selection is probably the only factor which indirectly may improve overall survival at present: Curative surgery should only be attempted in patients with limited extent of their disease, patients with locally advanced disease should be allocated for neo-adjuvant therapy, while the remaining patients should be referred for palliative measures. This thorough evaluation and subsequent treatment assignment should also be used in the identification of uniform patient cohorts for new treatment protocols. Thus, accurate pretherapeutic assessment of the disease stage and resectability are major cornerstones in the attempt to provide optimal and individual treatment strategies, and in order to enable evaluation of new treatment regimens in UGIC patients. But despite the importance of accurate pretherapeutic assessment being repeatedly emphasized insufficient staging has been – and is still accepted as – leading to high rates of explorative surgery(1-5) as well as heterogeneous selection of patients for new treatment trials.
Due to lack of substantial progress in UGIC treatment results and the disappointing staging evaluation the author evaluated the use of endoscopic ultrasonography (EUS) in his Ph.D. thesis. The author concluded that EUS as a single imaging modality provided detailed information that hitherto had been inaccessible. EUS was considered a significant progress regarding the loco-regional assessment of stage and resectability, but it was also evident that EUS alone was incapable of providing all the necessary information. In addition, there were no evidence regarding the EUS safety

profile, patient tolerance of the procedure and no data on the clinical impact of both EUS and EUS guided fine-needle aspiration biopsy (EUS-FNA) in UGIC patients.
Therefore, the author choose to conduct additional EUS trials and to test the use of EUS-FNA, laparoscopy (LAP), laparoscopic ultrasonography (LUS) and LUS guided biopsy in order to improve the overall pretherapeutic evaluation and thus the patient selection.

2. AIM

The aim of this thesis was to describe the sequential development, testing and clinical results of a new pretherapeutic evaluation strategy based on EUS and LUS.
More precisely it was investigated whether this new strategy was feasible, safe and cost-effective, the exact clinical role of EUS-FNA and LUS guided biopsies in this strategy, and whether a potential improvement in the pretherapeutic evaluation would have a clinical impact on patient management. The latter exemplified by improved selection of patient for radical or palliative resection, or by avoiding futile surgery in patients with advanced or disseminated disease.
The following topics were investigated and discussed in detail:

- Endoscopic ultrasonography (EUS) and EUS guided fine-needle aspiration biopsy (EUS-FNA) in the pretherapeutic staging and resectability assessment (Section 5.1)
- Treatment impact of EUS and the combination of EUS and laparoscopic ultrasonography (LUS)(Section 5.2)
- Cost-effectiveness of different imaging strategies in the detection of patients with non-resectable disease (Section 5.3)
- Combined pretherapeutic EUS and LUS as predictors of long-term survival (Section 5.4)

3. DEFINITIONS & METHODS

Operability, resectability and TNM-stage

The indiscriminate use of the terms “operability” and “resectability” in the literature may confuse the comparison of studies. Therefore, operability was defined as the patient’s physical and psychical ability to endure major surgery or medical treatment, and all patients were classified (ASA score, overall operability) during the first personal contact with the department. Basically, resectability (R-classification) is considered a supplement to the clinical and pathologic TNM staging systems. The R-classification is a strong predictor of the prognosis since it reflects the tumour status after treatment. The author introduced a second definition and use of the term resectability in order to compensate for the obvious shortcomings of the TNM system regarding pretherapeutic evaluation of UGIC patients. Not only does the TNM system change over time, but the TNM stage does not take into account the aspects and possible problems of different surgical approaches to tumour and/or lymph node dissection. More precise topographical details are often needed from a surgical point of view in order to provide optimal conditions for the choice of surgical approach, and this information may not be derived from the TNM classification alone (e.g. A T4 gastric tumor may involve the retroperitoneum or the spleen. The latter infiltration would be resected without any problems, but deep retroperitoneal infiltration of the celiac trunk area may render the tumor non-resectable). Therefore, the definitions of resectability used in this study represented a link between the clinically relevant tumour related details, pretherapeutic imaging and final outcome. Three different resectability groups were defined prior to the inclusion of the first patients(I) and these definitions were used consistently throughout the studies.
Despite the problems of the TNM system regarding the prediction of resectability all patients also had a TNM stage assigned based on pretherapeutic imaging. This was done in order to evaluate the ability of the imaging modalities regarding the overall extent of the cancer disease and to allow for a comparison with other studies. The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM classifications (3rd and 4th editions) were used including the changes made over time.

EUS and EUS-FNA

EUS was performed in an out-patient setting in the majority of patients using local anaesthesia and intravenous sedation. No prophylactic antibiotics were given. No cytopathologist was present during EUS-FNA. FNA punctures were performed using a minimum of three needle passes or until the endosonographer by macroscopical inspection of the aspirated material felt assured that sufficient material had been obtained. Patients were monitored during the procedure by pulse rate, blood pressure and saturation, and after the procedure the patients were monitored by specially trained nurses until discharge. Immediate complications were prospectively registered. Information about EUS findings as well as a preliminary treatment plan was provided by the endosonographer before patient discharge. All EUS examinations were performed with linear echoendoscopes (Pentax FG-32UA, FG-36, FG-38UX or EG-3870UTK, Pentax Hamburg, Germany) in case EUS-FNA was needed. The echoendoscopes were connected to the Hitachi EUB-565, the Hitachi 6500 or Hi Vision 900 scanner units (Hitachi, Switzerland). EUS-FNA was only performed if a positive (malignant) finding would change the subsequent patient management. Dedicated needles used for EUS-FNA were 22 Gauge (G) or 19-G in diameter (GiP Medizin Technik, Germany, and Cook Medical, Denmark). All EUS examinations were described in detail and ended by a conclusion regarding TNM-stage and resectability. Details on biopsy indications, needle monitoring, target size and location, numbers of biopsies and needles, technical problems as well as immediate complications were prospectively registered, and late complications (after discharge) were registered during follow up.

Laparoscopy, LUS and LUS guided biopsy

Laparoscopy and LUS was performed under general anaesthesia using the “two-trochar” technique(6). One 12mm trochar was placed close to the umbilicus on the left side and an additional 12mm trochar was placed laterally and sub-costally in the upper left abdominal quadrant. The umbilical trochar was mainly used for the camera, whereas the upper left trochar was used for laparoscopic biopsy, LUS and LUS guided biopsy. LUS was performed using a dedicated curved array laparoscopic transducer (Type 8566 or 8666; BK Medical, Copenhagen, Denmark or Hitachi EUP-OL531, Hitachi, Switzerland). The transducers were connected to a Lynx 3101 scanner unit (BK Medical, Copenhagen, Denmark), the Pro Focus UltraView unit (BK Medical, Copenhagen, Denmark) or the Hitachi EUB 8500HV scanner unit (Hitachi, Switzerland).
Needles and a detachable biopsy device for LUS guided fine-needle aspiration (22-G) or trucut biopsies (19-G, 20-G) were developed in cooperation with BK Medical, Copenhagen, Denmark. “Free-hand” LUS guided trucut biopsies through the abdominal wall were performed using a 19-G automatic biopsy

needle device (BioPince, Angiotech, USA). Laparoscopic and LUS guided biopsies were only performed if a positive (malignant) finding would change the subsequent patient management, and the biopsy procedures were repeated until the surgeon felt assured that sufficient material had been obtained. All examinations were described in detail and ended by a conclusion regarding TNM-stage and resectability. Details on biopsy indications, needle monitoring, target size and location, numbers of biopsies and needles, technical problems as well as immediate complications were prospectively registered, and late complications (after discharge) were registered during follow up.

Impact

There is no universal definition of "Impact" in the medical literature. Impact is explained by "Strong impression or effect"(7), and therefore impact definitions may be modelled to suit all kinds of medical trials. However, impact studies on pretherapeutic imaging intended to monitor clinically relevant changes in patient management can provide more information than accuracy studies in matters of health technology assessment(8). Therefore, impact was defined in the present study as the clinical effect of changing an evaluation strategy or adding a new imaging modality or biopsy procedure to an existing strategy. The clinical effect was measured in different terms according to the problem in question (e.g. number of patients avoiding futile laparotomy or number of patients getting the right diagnosis and treatment).

Cost-effectiveness

Cost-effectiveness analyses have become an essential and integrated part of modern patient management due to the steadily increasing number of treatment options as well as due to the limited financial resources within the health care system. However, the definitions of cost and effect as well as the way the calculations are performed are highly variable, and should be considered in detail during interpretation(9). The author chose to measure the actual costs of performing the different procedures involved, and these costs were retrospectively calculated from the perspective of the budget-holder (department level), whereas the indirect costs were not included. The measure of "Effect" was defined as the number of patients with non-resectable UGIC disease found through the diagnostic strategy in question. An incremental cost-effectiveness was added to the analysis in order to investigate the additional extra cost per extra patient detected with non-resectable disease when moving from one imaging strategy to another.

Prediction of long term survival

Accurate pretherapeutic estimates of survival are essential during patient information, treatment planning and when selecting patients for new treatment trials. Retrospective data have shown some concordance between pretherapeutic EUS based staging and the pathologic TNM stage, and this has been used to evaluate the prognostic abilities of EUS(10, 11). Due to the aforementioned limitations of the TNM system and the lack of complete staging by single imaging strategies it was evaluated if pretherapeutic stage and resectability stratification by EUS and LUS related to the observed prognosis in UGIC patients.

Data registration and analysis

From December 1991 all EUS examinations were prospectively entered into a computer database. Since 1992 all patients who were treated for UGIC in the Upper GI Section, Department of Surgery, at Odense University Hospital, were also registered in a prospective UGIC database. This registration included pretherapeutic evaluation, treatment and follow-up. Both databases, which were continuously updated and validated, were used as a supplement in pro- and retrospective studies, especially regarding validation of data and in cases of missing data. After the introduction of LUS the results of these examinations were included in the databases as well. Unique case record forms and data sheets were created and used for each of the included studies, and during follow-up, confirmation of diagnosis and pathological/cytological findings, autopsy reports, death certificates, patient records etc. were reviewed through central databases or by hand. Statistical analysis was performed by hand or using Excel, SPSS or STATA. Details on the statistical methods are listed in the publications. The level of significance was set at 0.05 throughout all studies.

4. ETHICS

Patients were enrolled in the studies in accordance with protocols approved by the regional Ethics Committee. Studies initiated after the first half of 2007 were also registered in the ClinicalTrials.Gov. The databases were approved by central authorities according to law.

5. RESULTS AND DISCUSSION

5.1 Endoscopic ultrasonography (EUS) and EUS guided fine-needle aspiration biopsy (EUS-FNA) in the pretherapeutic staging and resectability assessment

Diagnostic aspects

The value of EUS and EUS-FNA in the primary diagnosis of oesophageal and gastric cancer was limited(III) as the diagnosis had been established by standard endoscopy and biopsies. EUS alone was important in the diagnosis of pancreatic cancer due to the ability to detect small lesions not seen by other imaging modalities(12-14), but the diagnostic gain of adding EUS-FNA depended on the clinical setup in which the patients were evaluated. The author found that EUS-FNA was clinically relevant in 25% of the patients with pancreatic lesions and malignancy was confirmed in 86% of these patients(III). The reported diagnostic accuracies of EUS-FNA were similar to our findings(12, 13, 15, 16), but a comparison of data regarding how often EUS-FNA was clinically indicated was impossible to perform. Different clinical routines (e.g. referral pattern, previous biopsy attempts), selection bias (e.g. cancer prevalence, tumor size) and attrition bias (e.g. inconclusive/inadequate biopsies) were the major reasons for this(III,13, 15, 17-26). To illustrate the potential diagnostic gain of EUS-FNA Gress et al.(20) evaluated 102 patients with previous negative CT biopsy or negative ERCP cytology. With a cancer prevalence of 60% EUS-FNA had a sensitivity of 93%, a specificity of 83% and 8% non-diagnostic biopsies.

The reported high predictive values of EUS and EUS-FNA have perhaps tended to reduce the attention towards the number and potential consequences of a false negative or false positive EUS-FNA. Fortunately, the latter is generally reported low(25, 27, 28) or non-existing(III,13, 16, 20) and may of cause be attributed to the FNA sampling and evaluation technique in general rather than being performed under EUS guidance.

In conclusion: From a diagnostic point of view EUS and EUS-FNA were most important in pancreatic lesions.

Staging and resectability assessment

TN staging based on EUS only provided accuracies above 80% for esophageal and gastric cancer when compared with histopathological or intraoperative findings. The interpretation of the pancreatic cancer results and subgroup analyses (e.g.T1-4) was limited due to small numbers, but overall data were comparable to other studies. EUS had low sensitivities for M1 disease in gastric and pancreatic cancer patients due to the inability to detect peritoneal carcinosis and liver metastases, whereas the M-staging in esophageal cancer provided a 96% accuracy in patients with a complete examination(I).

EUS alone was also tested for its ability to predict resectability. Using predefined treatment groups EUS had an overall accuracy of 86% (CI=75-97), 91% (CI=83-99) and 84% (CI=77-91) in esophageal, gastric and pancreatic cancer patients, respectively(I,6). However, these figures dropped significantly in all three groups (p= 0.0001) when EUS resectability assessment was re-evaluated in a larger study under routine conditions(VI). The two series were comparable except for the number of patients in the R1/R2 group which were significantly lower in the latter (16.3% vs 9.3%, p=0.044). The most obvious explanations were a drop in test performance over time, which is often seen when moving from a protocolled study to everyday routine, or the fact that the EUS evaluation in the latest study could be supplemented by LAP/LUS. Criteria of non-resectability, use of endobiliary stenting, local experience and preferences constitute major selection problems in data regarding pancreatic cancer, not only in surgical studies, but also in the evaluation of imaging modalities(14, 29, 30). This should be reflected in the interpretation of EUS, CT and MRI results, especially during comparison between institutions. Coherent with other data the author found EUS superior to CT in detecting local non-resectability(I,VI, 6, 29, 31-33), but studies demonstrating more equivalent results(34-36) and a supplementary effect of a combined approach(37-39) have also been published.

In conclusion, TN-staging based on EUS provided accuracies above 80% for all cancer types, but the pancreatic cancer results were based on a small number of patients. The EUS resectability assessment was considered accurate, but significantly lower values were observed when EUS was re-evaluated under routine settings.

EUS-FNA

With the introduction of EUS-FNA came the possibility to confirm malignancy in N1 and M1 disease which had been suspected during the EUS examination. Whereas the latter would have an impact on patient treatment, the confirmation of N1 disease would mainly be interesting in relation to a potential improvement of the EUS N-staging performance. This was not the intention of the present work, but data have suggested that EUS-FNA could improve overall N-staging accuracy(40-43), and that EUS-FNA was superior to helical CT(44, 45).

In the majority of UGIC patients, where several lymph nodes fulfilled the criteria of malignancy, biopsies were probably not needed(I). This was supported by the fact that the same criteria, which indicated a (high) risk of malignancy, were also used in EUS-FNA studies to select lymph nodes for biopsy(40, 41, 43, 46, 47). Additionally, performing EUS-FNA in all visualized lymph nodes would be time consuming, expensive, uncomfortable and potentially dangerous to the patient. Vazquez-Sequeiros et al(48) evaluated a selective use of EUS-FNA in the nodal staging of esophageal cancer by comparing the four standard criteria suggesting malignancy with standard criteria plus additional criteria (EUS identified celiac lymph nodes, >5 lymph nodes, or EUS T3/4 tumor). Thus, like others(40, 41, 49, 50) indirectly taking the EUS based evidence of advanced disease into consideration. Using ROC curves they found that the modified EUS criteria were more accurate than the standard criteria, and by employing the former they could have avoided EUS-FNA in 41% of the patients. Using a similar approach additional factors could probably be identified and used to select patients for EUS-FNA in gastric and pancreatic cancer as well.

The effect of lymph node micro-metastases on EUS and EUS-FNA test performance is unknown, and the impact on survival may vary among UGIC patients(51-53). Different cytological techniques have been used on EUS-FNA aspirates, but the potential impact and cost evaluation have not been investigated(54, 55). Overall EUS-FNA demonstrated a relatively small but significant impact on the staging/resectability assessment and subsequent management of UGIC patients. There were no differences between the impact in esophageal, gastric and pancreatic cancer, and the EUS-FNA verification of distant lymph nodes metastases was the major contributor to these results(III). Again, the various study designs and definitions provided different results and made comparison with other studies difficult(12, 44, 56, 57) but the test performances of EUS-FNA were comparable(12, 43, 56-59). In general, the more stringent biopsy criteria the lower the impact (e.g. more aggressive surgery reduced the need for EUS-FNA)(56). The continuous use of stringent biopsy criteria allowed for an indirect analysis of results over time and thus an estimate of data reliability. The number of patients where EUS-FNA was indicated and performed due to signs of disseminated disease remained constant during two different time periods (p=0.25), indicating adherence to the stringent biopsy criteria also outside a protocolled setup(III,VI).

The author's data illustrated the complementary use of CT/US and EUS-FNA to some extent. From the total number of lesions biopted for staging/resectability purposes 15% (7/46) had been suspected previously by CT/US, and this could have favoured the localization and detection rate of EUS(III). By excluding pancreatic lesions this figure increased to 27% (7/26) suggesting a higher complementary effect of EUS and CT/US in esophageal and gastric cancer regarding the staging/resectability impact of EUS-FNA. This complementary effect was further illustrated by a EUS detected, but EUS-FNA inaccessible lymph node, where CT-guided biopsy was able to confirm malignancy, or the two cases where EUS pointed towards liver metastases and repeated US with FNA confirmed M1 disease(III).

It was important to note that M1 disease could be detected by EUS(I) and confirmed by EUS-FNA, since M-staging has been considered impossible by EUS, and it was also interesting that M1 disease could be detected and biopted in pleural fluid, ascites and the liver(III). The latter findings were later confirmed in larger studies(60, 61), and EUS seemed able to visualize M1 lesions not detected by CT(III,62). EUS-FNA was performed in patients where EUS had detected a lesion which according to the UGIC disease and localization in question suggested potential M1 disease. Thus, EUS alone had raised the suspicion of disseminated disease, and the question whether or not EUS-FNA actually improved EUS results has also been addressed by others, but without any definitive answer(57, 59). From a clinical point of view the answer seemed straight forward: If the patient was to be denied attempted curative surgery based on for instance lymph nodes at the celiac trunk, then a malignant biopsy would be necessary in order to avoid the risk of a false positive finding. Similar, if the

patient was scheduled for neo-adjuvant therapy or palliative chemotherapy the oncologist would require a biopsy before starting the treatment. Thus, EUS-FNA confirmation again would be the preferred strategy if a change in patient management would be the consequence of malignant cytology. Data on the clinical consequences of false positive and negative EUS-FNA are lacking as mentioned above, but recent experience from a large tertiary referral centre focused on the potential causes of false positive EUS-FNA(27). The majority of these mistakes were made in peri-esophageal lymph nodes, and the clinical consequences were modest. Detailed analyses of the biopsies pointed towards epithelial cell contamination, EUS sampling error and pathological misinterpretations as the causes of these false positive lymph node diagnoses, and special attention seemed warranted when performing EUS-FNA in the presence of a luminal neoplasm.
Despite the overall positive results, complete M-staging by EUS and EUS-FNA must still be considered limited by topographical access. CT(63-65), MRI(66) and perhaps PET-CT(67) may provide non-invasive imaging of areas inaccessible to EUS, but these techniques have limitations as well(III,VI,6, 12, 13, 63, 64, 67).
In conclusion: The number of patients where EUS-FNA was indicated and performed remained constant over time. EUS-FNA demonstrated a small (12%) but significant impact on the staging/resectability assessment and subsequent patient management, and the EUS-FNA verification of distant lymph nodes metastases was the major contributor to these results. EUS with EUS-FNA were insufficient in detecting all patients with locally advanced or disseminated disease.

Complications

The author found significantly more complications related to the EUS procedure in patients with a malignant diagnosis than in those with a benign disease (p=0.01), but this could not be attributed to EUS-FNA(V). Overall EUS related morbidity (0.61%, CI: 0.30-1.17) and mortality (0.07%, CI:<0.01-0.42) in UGIC patients were comparable to previous data and lower than seen after ERCP(68, 69). A similar sized, prospective study found a zero percent mortality and a morbidity of 0.5% (CI:0.1-1.5) in UGIC patients, but these patients accounted for only 19% of the total number of examinations(70), and they did not encounter more complications than patients with benign diseases (p=0.19). A systematic review of EUS-FNA in more than 10.000 patients reported of a mortality of 0.02% and a procedure related morbidity of 0.98%(71). Comparison of studies on EUS and EUS-FNA related morbidity was difficult due to the lack of consensus on definition, classification, and grading of endoscopic complications and due to the different study designs.
Two-thirds of the complications occurred in esophageal cancer patients as potential life threatening perforations. These were probably inevitable and not unique related to the EUS procedure, since endoscopic examination of the esophagus (with or without tumor stenosis) will always harbour the risk of perforation(72). Rigid bouginage should be minimized prior to EUS, but this alone may not eliminate the risk of perforations(V). Other studies reported similar results regarding EUS related esophageal perforations, and high patient age, difficult intubation and the experience of the endosonographers were important risk factors(73, 74). Immediate complications related to EUS-FNA of pancreatic lesions were reported on a low and acceptable level(V,71, 75). However, EUS-FNA induced inflammation causing local non-resectability in a pancreatic cancer patient(76), and the risk of needle-track seeding(71) or picking up luminal cancer cells by EUS-FNA(77) are new and potentially important observations, but the exact extent of the problem is unknown.

Patient tolerability

Close post-procedure monitoring disclosed minor transient complaints in one-third of the patients, but re-admission (0.7%, CI:0.2-2.6) or contact to the patients GP (6.1%, CI:3.9-9.6) due to complaints thought to be related to the EUS procedure were seldom(V,78). The use of intravenous propofol sedation(70, 79) and a shorter follow-up may explain the lower number of post-procedure complaints in another large EUS study(70).
The duration of the procedure, the use of large calibre echoendoscopes and restrictive use of intravenous medication may explain why half of the patients had moderate to severe discomfort, which was higher than the reported rate of pain and anxiety. Previous endoscopic experience in the majority of patients seemed to have had a positive impact on the rating of (severe) anxiety. The examinations were performed by 5 different persons during the study period, but the potential influence of EUS training and endoscopic experience was not evaluated.
More than 90% of the patients (cancer or not) were prepared to undergo another EUS examination if indicated. This could be the result of the information provided before and after the procedure, the examination technique and the sedation, previous endoscopic experience, or a combination of these and other factors(80). It was impossible to evaluate this in detail, but the personal interview could have been a source of positive bias (e.g. “Social desirability response bias”)(81). A second interview 8 days later provided the same results as recorded immediately after the EUS procedure, and the direct contact in both interviews may have reduced the risk of bias regarding the reported rate of complaints as well as securing a high response rate(81), and a complete overview over post-EUS problems(78). Officially validated endoscopic questionnaires(80, 81) were not used in all studies(V,82), and this could also have influenced the outcome. However, the positive data seemed robust (“Pain”, “Anxiety”, “Satisfaction”) and consistent over time(V), and the number of responders were high compared with other trials(80-82).
The conduction and evaluation of patient satisfaction surveys are complex and no standardized patient satisfaction questionnaire exists(83). The majority of patients were satisfied with the level of information provided before and after the examination. All patients with UGIC were informed of the EUS findings and of the planned treatment strategy immediately prior to discharge. Thus, these patients had received optimistic or more serious information after the first interview, but before the second interview a week later. The effect of a “positive” or “negative” EUS result on patient satisfaction was not evaluated, but there were no differences between the results of UGIC patients and patients with benign diseases. UGIC patients had often received little or no information about their disease prior to the referral, and the detailed (pre- and) post-EUS information may have had a positive influence on patient satisfaction.
Preliminary data have suggested that patients preferred information immediately after the procedure, but also that some of the information was forgotten by the patient within just one day(82). Retrograde amnesia due to the extensive use of midazolam may explain these findings, but the patients’ own interest in (or capability of) receiving potentially bad news could be one of several related factors(84). The recent introduction of Nurse Administered Propofol Sedation (NAPS) in our department may reduce

the problem of amnesia and may further improve patient tolerability and satisfaction.
In conclusion: Minor transient complaints after the EUS procedure were seen in one-third of the patients. EUS related morbidity and mortality in UGIC patients were 0.61% and 0.07%, resepectively, and this was comparable to later series. Two-thirds of the complications in this study occurred in esophageal cancer patients as potential life threatening perforations. EUS-FNA was not associated with more complications than EUS alone. The EUS procedure was generally well tolerated and the majority of patients were prepared to undergo another EUS examination if indicated.

5.2 Treatment impact of EUS and the combination of EUS and laparoscopic ultrasonography (LUS)

Impact of EUS on patient treatment
There are several factors which may influence the impact evaluation of EUS in the routine treatment of patients with UGIC. Like other new imaging modalities EUS accuracies tended to decrease over time(I,VI,6, 85, 86), but methodological differences and publication bias are potential sources of error(I,86, 87) in the comparison of studies.
The clinical decision may prove difficult if the provider or the order of images represent a different speciality than the person making the final treatment decision(88). Being unfamiliar with the terminology, advantages and limitations of an imaging modality could influence the clinician's decision regarding the primary or supplementary use of such a technology(88-90), and this may coincide with the reported low use of EUS(90, 91). Finally, patient expectations, preferences and symptoms could also influence treatment decision independent of pretherapeutic imaging findings. Thus, the evaluation of EUS impact on treatment decision in UGIC patients should be conducted in a routine setting, among physicians with detailed knowledge of both imaging modalities and treatment, and in a setting where all relevant clinical information is available. Preliminary studies on post-procedure multidisciplinary team conferences (MDT's) where treatment related patient stratification was based on all available patient data rather than a single imaging modality(85, 92, 93) seemed to confirm the benefits of this approach. In accordance with these aspects the author found that adherence to predefined treatment options were necessary in order to measure potential changes in patient handling. However, this also limited the possibility of individual treatment plans in complicated cases, and thus provided a potential source of bias. "Adjuvant therapy" was added and "Explorative laparotomy" was substituted by "Laparoscopy" in the predefined treatment options, when the impact measurement moved from department levelI to an international comparison(VII). This reflected the increased use of adjuvant therapy and staging laparoscopy in the latter study period, but otherwise the treatment options were comparable. The treatment decision was changed in one-third of the patients with the results of the EUS available(VII), and as expected this was mainly towards non-surgical and palliative strategies(I,VII,94). Although the inter-observer agreement was low EUS promoted the concordance from "poor" to "fair" with the highest scores in esophageal and pancreatic cancer assessment. This could be explained by the limited treatment options in these patients if advanced cancer disease was suspected. Alternatively, EUS impact in esophageal cancer patients could be attributed to both the detection of disseminated disease as well as the identification of early tumors which made neoadjuvant therapy unnecessary(95). However, this did not change the overall rate of EUS impact.
In the context of the reported changing test performances of EUS the potential impact of a wrong EUS conclusion on treatment decision was interesting. There were no significant changes over time regarding the number of wrong EUS conclusions (12.2% vs 17%, p=0.34) or the number of cases where the surgeon(s) reacted with a wrong decision to this (8.1% vs 7%, p=0.8). However, the consequences of the latter resulted in a higher futile laparotomy rate in the early data (11.8% vs 66.7%, p=0.003) suggesting a learning curve(I,VII). The observed "misguiding" even in correct EUS conclusions also indicated a learning curve regarding the formulation of the EUS description itself(I), but it is doubtful whether adherence to minimal standard EUS terminology(96) would be of any benefit. No studies seemed specifically designed to investigate the rate and impact of wrong EUS conclusions, and future prospective studies should focus on both causes and consequences.
The false negative EUS conclusions leading to futile laparotomies reflected the problem of detecting disseminated intraabdominal disease using EUS and CT. But false positive EUS assessment of non-resectability could have even more serious clinical consequences, and this risk was estimated to be between 0 and 2%(I,VII,6, 39, 97, 98), whereas the risk of false positive CT findings seemed higher(39, 92, 99, 100). Again, the comparison of EUS dominated versus CT dominated strategies was biased by local preferences and experience(87), and this could also have influenced the author's results.
In conclusion, the impact of EUS on treatment decisions in UGIC patients seemed lower than would have been expected from the test performance of EUS. Several confounding factors and bias as well as limitations in study design made comparisons difficult and may also have influenced overall impact assessment. The clinical effect of a wrong EUS conclusion was limited, but EUS false positive resectability assessment could have denied the patients of a potential curative resection in up to 2% of cases.

Combined evaluation using EUS and LUS
Realising the limitations of EUS and CT, and in order to reduce the number of futile laparotomies, laparoscopy (LAP) was introduced as part of the pretherapeutic evaluation strategy(100-103). However, since laparoscopic dissection was unable to compensate for the inability of LAP to evaluate lesions beneath the visible surfaces(101, 104, 105) the author added laparoscopic ultrasonography (LUS) to the LAP procedure(6).
The addition of LUS to the US and CT based imaging strategies improved the TNM staging accuracy(106, 107). Regarding resectability assessment the combination of EUS and LUS predicted R0 resection in 91% (CI:85-96) of the patients, thus significantly increasing the overall accuracy when compared to EUS alone (69% (CI:62-77))(VI). Smaller LUS studies have reported similar results(108-111), but data based on a strategy where EUS provided the major selection of patients for LUS were unique and no data were available for comparison. The author's data did not allow for a comparison with CT based imaging regarding the prediction of R0 resection, but there was a striking worldwide homogeneity among high-volume cancer centres reporting R0 resection rates of 70-75% when based mainly on CT findings(VI). The combined approach provided results similar to R0 resection regarding the prediction of R1/R2 resections but the confidence intervals were wide (CI: 79-100) due to the limited number of patients. Comparison with other studies was difficult since these

patients were often reported as part of the intended radical resections group with no specific data related to the accuracy of the pretherapeutic imaging regarding the palliative group. This was reflected in the reported lower R0 resection rates, and strategies based on trial resection may have a significantly negative impact on the importance and results of pretherapeutic imaging. Due to the limited number of patients receiving neo-adjuvant therapy the potentially negative impact(112) on the test performance of the combined approach was not evaluated. Thus, the clinical effect of adding LUS to an existing imaging strategy depended not only on the test performance of the previous imaging modalities(VI,113, 114), but also on the parameter(s) used to monitor the effect(92, 110, 115) and local treatment preferences(4).

After the combined EUS and LUS strategy was introduced the author considered a futile laparotomy rate below 5% to be acceptable(VI,IX). Excluding patients who needed surgical bypass reduced the number of futile laparotomies to 2.4%(VI) and similar observations were made in other studies(115, 116). Again, a more aggressive surgical treatment approach would have changed the definition of futile laparotomies and questioned the fundamentals of pretherapeutic evaluation, but increasing data support the use of minimal invasive staging modalities prior to open surgery(117, 118).

Like EUS, LUS probably also has a learning curve, but the interobserver agreement during LUS was good(119), and this could perhaps be attributed to the EUS experience of the persons performing the laparoscopic procedure. Three-dimensional LUS and the use of two observers instead of one seemed able to increase the accuracy of LUS regarding the resectability assessment, but this was not statistically significant(119).

The role of LUS in the combined imaging strategy was well defined, but - although not recorded - LUS indirectly also helped identifying patients who would not withstand major surgery owing to co-morbidity or cancer related poor overall status(100, 105). Finally, the reported complication rates including port site metastases(113) related to the LUS and LUS guided biopsy procedures were close to zero(IV,VI,VIII,117).

In conclusion: The sequential use of EUS followed by laparoscopy with LUS provided an accurate designation of patients into predefined and clinically relevant treatment strategies, and almost obviated the need for futile laparotomies.

LUS guided biopsy

Using the "two-trochar technique" it was possible to obtain laparoscopic biopsies from peritoneal and superficial liver lesions(102), but lesions located within the liver and retroperitoneum were inaccessible and transabdominal biopsies guided by LUS ("Free-hand biopsy") were difficult to perform. In order to be able to perform LUS guided fine needle aspiration biopsy (LUS-FNA) and LUS guided trucut biopsy under direct ultrasonographic needle monitoring the author's group developed a detachable biopsy device which could be attached to a dedicated LUS-probe(IV,120). Preliminary data suggested that the biopsy system provided sufficient needle monitoring and penetration as well as concordance between the selected target and the obtained biopsies. The LUS biopsy procedure was quick and safe and provided additional clinically valuable information despite a relatively low rate of sufficient material(IV). The latter indicated a learning curve, and a study performed under routine conditions with an estimate of the potential impact of LUS guided biopsies was needed. Therefore, the author monitored the indications and use of LUS guided biopsy in a prospective study of 209 consecutive patients with bioptically verified or suspected UGIC - including liver and bile duct tumours(VIII) – using the same stringent criteria as during EUS-FNA(III). LUS biopsies were indicated in 12% (CI:8-18) of the patients with a final malignant diagnosis, and the major overall indication (55%) was lack of biopsy from the primary tumour, whereas the detection and verification of new or previously suspected metastases accounted for 26% and 19%, respectively. Adequate material was obtained in 95% of the biopsies despite being taken by six different surgeons. The overall combined impact of laparoscopic and LUS guided biopsy in patient management amounted to 27% (CI:22-34), and this figure remained unchanged if only esophageal, gastric and pancreatic cancer patients were included (33/109=30%, CI:22-40).

This finding may reflect both a stringent biopsy indication, but also that patients who were selected by EUS for LUS and surgery had a high chance of having a resectable lesionI. Previous data on the impact of standard laparoscopy showed large variations(121), but the 15% in our study combined with an additional 12% sustained by the LUS biopsies seemed a relevant estimate of the potential impact of laparoscopic and LUS guided biopsy in UGIC patients. The clinical significance of the latter technique was emphasized by the fact that these biopsies were the only way to obtain true benign biopsies in more than half of the patients who turned out to have a benign disease.

In conclusion, laparoscopic and LUS guided biopsies were safe and important adjuncts to the routine LAP/LUS procedures. The stringent biopsy criteria employed and the detailed preoperative selection of patients for LAP/LUS resulted in a need for biopsy in approximately one-third of UGIC patients.

5.3 Cost-effectiveness of different imaging strategies in the detection of patients with non-resectable disease

Methodological aspects

Progress in cancer research is mainly reflected in patient outcome, whereas resource consumption and impact on health care budgets are seldom reported in clinical trials. Cost-effectiveness analyses (CEA's) may provide reliable data for economical conclusions and comparison between studies, but CEA's should adhere to several methodological criteria. This has been consistently emphasized in guidelines, but the number of criteria, their importance and the quality of the reported studies varied significantly(122, 123). A checklist consisting of 10 important methodological items has been suggested and used in relation with the evaluation of CEA's(9). Additionally, the National Health Service (NHS) Centre for Reviews and Dissemination (York, UK) has provided an open-access database covering structured abstracts of CEA's since 1994 (www.york.ac.uk/inst/crd) in order to promote critical appraisal of economic evaluations. A recent review of 110 surgical CEA's found that only 9% included all 10 major items suggesting a complete economical evaluation, whereas on average only 4 of the 10 items were addressed in the remaining studies(9). A continuous review by NHS seemed to support these findings (www.york.ac.uk/inst/crd).

Clinical aspects

Strategies using CT plus US, laparoscopy alone and a combination of the three were all dominated, whereas EUS and LAP/LUS or combinations including one of these strategies were cost-effective(II). The addition of EUS to CT (or MRI) has been recommended from a clinical point of view(38, 39, 67), and in the au-

thor's retrospective study this also resulted in a net saving and a cost-effective strategy.
The observed low effect of CT plus US(II,VI,105) could be questioned(35, 39, 63, 67), but increasing the effect would only have moved the combined strategy further (down) to the right and made it even more attractive from a cost-effective point of view. Thus, from the view of the local budget-holder the combined use of non-invasive procedures would have been attractive. However, CEA's should also consider the clinical consequences of cost-effective strategies, and up to 20% futile explorative laparotomies would be the result of a strategy based on CT, US and EUS. The combination of EUS and LAP/LUS reduced this to a few percent(II,VI,6, 115), and despite the increased expected cost per patient this strategy would still be cost-effective. The confidence in this conclusion would have increased if a sensitivity analysis had been listed, but although not reported our data proved resistant to significant changes in both costs and effect (e.g. Doubling the effect of CT+US (60%) and reducing the cost of CT+US by 50% (563US$) would still leave CT+US as a dominated strategy). Additionally, the reported median length of hospital stay in relation to explorative laparotomy and laparoscopy was comparable to other data(101), and the diagnostic accuracy of EUS+LAP/LUS regarding the detection of non-resectable patients remained unchanged over time(VI,IX,6). Discounting and evaluation of long term costs were not relevant in the present study. The inclusion of indirect costs was outside the scope of the study, but the figures may have supported the author's findings if the increased morbidity related to futile laparotomies(101) was reflected in the indirect costs.
LAP plus LUS was cost-effective regarding the identification of patients with non-resectable disease, but as LAP/LUS is unable to assess tumors or metastases outside the abdominal cavity it would seem unethical and costly to evaluate an unselected population with this invasive procedure only. A sequential use of non-invasive screening followed by more invasive methods in selected patients should be pursued(100, 109, 113).
Only a few CEA's regarding UGIC patients are available, and design and estimates of costs and effect data were difficult to compare. EUS alone continued to be robust and cost saving in a sensitivity analysis of patients with esophageal cancer although the EUS detection of patients with disseminated disease contributed with only 12%(95). The combination of EUS and LAP resulted in a reduced rate of futile laparotomies in pancreatic cancer patients, and treatment allocation using EUS was more cost-effective than an angiography based strategy(115), but LUS and helical CT were not included in this CEA. In a decision model based on available data from the literature LAP/LUS remained essential for a significant lower cost per life-year gained in patients with pancreatic cancer, and this was a constant finding under various scenarios(124). EUS-FNA seemed effective in providing cost savings in the same type of patients but no CEA was performed(12, 125). EUS-FNA plus PET was more cost-effective than EUS-FNA plus CT and other strategies in the assessment of esophageal cancer patients and provided more quality-adjusted life-years(126). The data were robust to sensitivity analyses and underlined the advantages of combined strategies which included the use of EUS. Despite some study limitations EUS-FNA also seemed cost-effective in these patients(127).
In conclusion, the combination of CT (plus US) with EUS was cost-effective in the detection of patients with non-resectable disease, but the combination of EUS and LAP/LUS almost eliminated futile laparotomies and at the same time remained cost-effective. The limited number of CEA's suggested that EUS should be used in some form of combined imaging strategy.

5.4 Combined pretherapeutic EUS and LUS as predictors of long-term survival
In the ideal concept of pretherapeutic evaluation the imaging modalities used should provide detailed information allowing optimal treatment decisions as well as a stratified estimate of the prognosis. Thus, as a natural extension to the evaluation of the clinical impact of EUS and LUS in UGIC patients the same combination was used to predict long-term survival based on both stage and resectability stratified data.

Prediction of survival
Numerous studies with different designs have evaluated the potential relation between pretherapeutic EUS findings and the prognosis in UGIC patients. Celiac(49, 128, 129) and peri-esophageal(49) lymph nodes, lymph node size(50), number of malignant looking lymph nodes(130), T-stage(10, 11), N-stage(129, 131, 132), and tumor area(133) are among the EUS factors identified as statistically significant related to survival. Since the addition of LUS to EUS and CT improved staging and resectability assessment it would be expected that the prediction of survival would improve as well. A comparative study was not performed (e.g. EUS versus EUS+LUS) based on the fact that no single imaging modality was sufficient for a complete evaluation(I,VI). But the combined approach provided relevant and significant stratification estimates of the prognosis in all three cancer types whether based on stage or on resectability assessment(IX). Since the combination of EUS and LUS was introduced by the author there were no data available for comparison, but improved patient stratification would allow a more detailed selection of patients for neo-adjuvant trails as well as providing a better estimate of the prognosis to be used during individual patient information(11).

Improving survival?
The use of EUS and LUS in UGIC patients has been tested in different ways, and a pretherapeutic evaluation based on both imaging modalities provided accurate and prognostically relevant information. The ability to predict R0 resection and to avoid futile surgery is an important progress when compared with traditional CT based pretherapeutic evaluation(VI, IX, 1). In theory, avoiding futile explorative surgery in patients with non-resectable or disseminated disease should provide a better outcome in these patients. Thus, out-patient evaluation, reduced hospitalization, fewer surgical complications and a shorter reconvalescens should allow a larger group of patients a rapid allocation to palliative treatment regimens, but there are only scarce and indirect evidence on this topic(8, 134, 135). Nor are there any data specifically evaluating whether or not EUS or the combination of EUS and LUS has improved overall or treatment related survival in UGIC patients. A nationwide randomized UK study on survival in esophago-gastric cancer patients with and without EUS ("COGNATE") was launched in 2004, but the final results are not expected until late 2011 (www.clinicaltrial.gov, March 2011). Retrospective data have suggested that the addition of EUS to the pretherapeutic evaluation provided an increased overall survival in esophageal(136, 137) and pancreatic cancer patients(138-140), but there are several sources of potential bias(8).
It is interesting, however, that pancreatic cancer patients selected for intended curative surgery by the combination of EUS and LUS

seemed to have a better long-term prognosis than reported in high-volume series based on CT imaging, and that this observation was not biased by a lower resection rate in the former study(IX,141).
The continuous problems of identifying true R0 resections in pancreatic cancer patients are essential for the understanding of this observation. Up to 80% of the resections classified as R0 has turned out to be R1 resections(142, 143), and obviously this will influence both the comparison of R0 resection rates and survival rates. Assuming that the quality of the performed surgery and the resection rates are comparable, it may be concluded that EUS and LUS allowed a better selection of the "true" R0 cohort than other imaging strategies (Figure 1). None of the patients in the author's study had received adjuvant/neo-adjuvant therapy as opposed to the majority of patients from other studies. Thus, the survival data may further improve in the author's population, and this would further support the EUS and LUS approach.

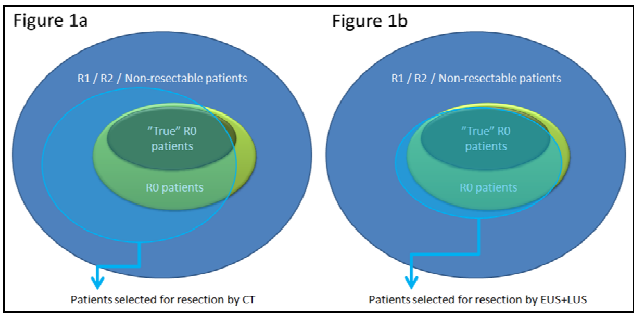

Figure 1. The blue circle illustrates the total patient cohort which consists of inoperable patients, patients with R1/R2/Non-resectable disease and patients who may undergo ("True") R0 resection. Figure 1a shows the selection of patients made by CT, whereas Figure 1b shows the patient cohort resulting from a selection by EUS and LUS. (The different circle sizes are not correlated to the number of patients in each circle).

National surveys on survival in esophageal and gastric cancer patients indicated a similar trend (www.gicancer.dk: DECV Annual Report 2008) in favour of patients selected by the EUS and LUS strategy.
The linking of pretheraputic evaluation and surgical outcome in PC patients may of course be speculative, but international data on survival have remained relatively stable over the last decade indicating that the approach to potentially curative treatment is unchanged. Thus, an observed improvement of survival while performing the same kind of surgery and adjuvant therapy may indicate that no fewer patients undergo treatment, but that patient selection may have improved. Only a randomized study would be able to confirm this, but considering the present result such a trial would not be possible for ethical reasons(136).
In conclusion, the combined pretherapeutic EUS and LUS patient stratification related significantly to the final prognosis in UGIM patients. EUS and LUS seemed superior to other imaging strategies regarding the identification of patients who may undergo a "true" R0 resection. Thus, EUS and LUS may have a positive impact on the prognosis in R0 resected UGIC patients.

6. STUDY LIMITATIONS

Randomized study design
The lack of randomization is an important study limitation relating primarily to Study I and VI. A randomized study comparing the standard pretherapeutic imaging strategy with the combined use of EUS and LUS would have provided data on both staging performance and clinical impact, and may have elucidated potential benefits of the new strategy based on more solid evidence. There are several reasons for not choosing this approach: During the first study it soon became evident that EUS both provided important additional local staging information and detected M1 disease not found during CT and US. The high futile laparotomy rates associated with CT based patient selection were considered ethically impossible to include in randomised trials, especially since EUS (and later EUS-FNA, laparoscopy and LUS) provided significantly better resultsI. Secondly, during the initial testing all research was focused on EUS being an alternative, single imaging modality approach to CT, whereas it later became evident that combined strategies were necessary, and that the different imaging modalities were supplementary rather than competitive. Local expertise in favour of advanced ultrasonography may also have influenced the outcome of a randomized study as well as the results presented in this thesis. However, the relative consistency of the results when moving from clinical trials, through strategy implementation towards routine use seemed to reduce the risk of such bias.

Patient tolerability and satisfaction
The evaluation of patient satisfaction and procedure tolerability are complex and include several potential pitfalls and possible bias. A large variety of study designs including both qualitative and quantitative methods may be used(144). Patients' ratings were evaluated using four-point scales, thus forcing the patients to make a choice as opposed to odd number scales which allow for a neutral position. There are no general consensus on this topic and the intervals between different values may not be equal(145). The four-point scale may have provided better results due to central tendency bias as well as acquiescence or social desirability bias. The reported rates of procedure related complaints may also have been positively influenced by the patient's focus on the diagnosis and the potential consequences of the EUS findings(144), and this could have affected the results obtained both during the first and the second interview. The potential impact of a nurse conducted interview was not evaluated.

Inter-observer agreement on impact
The lack of universally accepted definitions regarding kappa values, the influence of number of categories, the prevalence within each category, and the inability to compare reported kappa values between studies are well known limitations of this approach. Narrowing the confidence intervals by increasing the overall sample size or focusing on one cancer type only, may have strengthened the conclusions. The use of weighted kappa values would probably have increased the inter-observer agreement, and from a clinical point of view this would have made sense in some situations.

Cost-effectiveness
The retrospective study design implied some limitations. The internal validity of the effectiveness could not be evaluated, and the exact cost may prove different if prospectively recorded in detail. A true comparison with other studies was impossible to perform, and the issue of generalisability may be questioned due to the observed test performance of the included imaging modalities as well as the relatively narrow definition of costs. In addition, the potential impact of a detailed monitoring of a larger cohort over a longer time period remains unknown since other factors may become more relevant (e.g. discounting and indirect costs).

However, the study still fulfilled at least 7 of the 10 important methodological items suggested by the NHS.

LUS guided biopsy
The risk of port site metastases may have been underestimated due to the limited observation period.

Combined analysis of different cancer diseases
Several analyses were performed with UGIC patients as one entity, only(II,IV,VI). This approach may be criticized for accumulating and analysing data from cancer diseases with very different treatment strategies and prognoses. The decision to perform a combined analysis was deliberate since the studies focused on the overall imaging strategy rather than the individual cancer diseases. Significant differences between the included cancer types were noted and commented if relevant to the understanding and conclusion of the obtained results (e.g. diagnostic impact of EUS-FNA in pancreatic versus esophago-gastric tumors).

Scanning performed by the surgeon
All EUS and LUS procedures were performed by surgeons with special interest and experience in both curative and palliative treatment of UGIC patients as well as in advanced ultrasonography. In many cases the same surgeon performed both the preoperative EUS, the LUS evaluation and the resection. This experience, the surgeon's anatomical knowledge of problems related to local resectability, and the immediate feedback in cases of discrepancies between EUS, LUS and surgical findings, may be considered a positive bias in favour of this thesis. In addition, the majority of international EUS studies were performed by non-surgeons, and this may be part of the explanation for the lack of relevant studies for comparison as seen from the surgeon's point of view.

7. SUMMARY

Background and aim
A detailed and correct pretherapeutic evaluation of stage and resectability is mandatory for an optimal treatment strategy and results in patients with cancer of the esophagus, stomach or pancreas (UGIC). Curative surgery should only be attempted in patients with limited extent of their disease, patients with locally advanced disease should be allocated for neo-adjuvant therapy, while the remaining patients should be referred for palliative measures following a quick, lenient and correct pretherapeutic evaluation. This thorough evaluation and subsequent treatment assignment is also valuable in the identification of uniform patient cohorts for new treatment protocols as well as for the continuing comparison of research data. But despite the importance of accurate pretherapeutic assessment being repeatedly emphasized insufficient staging has been – and is still accepted as – leading to high rates of explorative surgery as well as heterogeneous selection of patients for new treatment trials.
Based on the results from the authors Ph.D. thesis he concluded that endoscopic ultrasonography (EUS) as a single imaging modality provided detailed information that hitherto had been inaccessible. EUS was considered a significant progress regarding the loco-regional assessment of stage and resectability, but it was also evident that EUS alone was incapable of providing all the necessary information. In addition, there were no evidence regarding the EUS safety profile, patient tolerance of the procedure and no data on the clinical impact of both EUS and EUS guided fine-needle aspiration biopsy (EUS-FNA) in UGIC patients.
Therefore, the author chose to conduct additional EUS trials and to test the use of EUS-FNA, laparoscopy (LAP), laparoscopic ultrasonography (LUS) and LUS guided biopsy in order to improve the overall pretherapeutic evaluation and thus the patient selection.
The aim of this thesis was to describe the sequential development, testing and clinical results of a new pretherapeutic evaluation strategy based on EUS and LUS.

Results
EUS and EUS-FNA in the pretherapeutic staging and resectability assessment

Diagnosis
The value of EUS and EUS-FNA in the primary diagnosis of esophageal and gastric cancer was limited, but EUS-FNA was diagnostically relevant in 25% of the patients with pancreatic lesions and malignancy was confirmed in 86% of these patients. Comparison with other studies were difficult since no other trials have specifically focused on the clinical need for EUS-FNA regarding the primary diagnosis and resectability assessment
Stage and resectability assessment
TN staging based on EUS only provided accuracies above 80% for all cancer types when compared with histopathological or intraoperative findings, but the pancreatic cancer results were based on a small number of patients.
A similar high overall accuracy of EUS regarding pretherapeutic resectability assessment dropped to a significantly lower value when re-evaulated in a larger study under routine settings. There may be several explanations for this observation, but the move from a protocolled trial to a routine setting and the possibility of using LAP and LUS in the latter material may have influenced the decision and thus the results.
The number of patients where EUS-FNA was indicated and performed remained constant over time, indicating adherence to the stringent biopsy criteria also outside a protocolled setup. EUS-FNA demonstrated a small (12%) but significant impact on the staging/resectability assessment and subsequent patient management. There were no differences between the impact in esophageal, gastric and pancreatic cancer, and the EUS-FNA verification of distant lymph nodes metastases was the major contributor to these results. Although EUS could detect and biopsy lesions not seen by CT, these imaging modalities were considered supplementary, but neither of these nor a combination of both was able to perform a complete evaluation of the TNM stage or the resectability.

EUS tolerability, complications and patient satisfaction
Minor transient complaints after the EUS procedure was seen in one-third of the patients, but re-admission (0.7%), or contact to the patients GP (6.1%) due to complaints thought to be related to the EUS procedure were seldom.
Overall EUS related morbidity and mortality in UGIC patients were 0.61% and 0.07%, respectively, and this was comparable to later series. Two-thirds of the complications in this study occurred in esophageal cancer patients as potential life threatening perforations.
The conduction and evaluation of patient satisfaction surveys are complex and with a high risk of bias. Despite the reported pain, anxiety and discomfort more than 90% were prepared to undergo another EUS examination, and a similar proportion of patients

were satisfied with the level of information provided before and after the examination.

Treatment impact of EUS and the combination of EUS and LUS
The impact of EUS on treatment decisions in UGIC patients seemed lower than would have been expected from the EUS test performance. This observation suggested that the final treatment decision was based on several parameters, but at the same time stressed the importance of stringent EUS statements based on predefined standards. Lack of knowledge regarding advantages and limitations of EUS, situations where EUS was performed by non-surgeons, confusing terminology and conclusions as well as different treatment traditions may have influenced the comparison of data on the clinical impact of EUS.
The inter-observer agreement on the treatment of UGIC patients was improved by EUS, and the ability to detect patients with non-resectable disease was the main reason for this among the one-third of all patients where EUS led to a change in the treatment approach.
The clinical effect of a wrong EUS conclusion was limited, but EUS false positive resectability assessment may have denied up to 2% of the patients of a potentially curative resection.
The combination of EUS and LUS solved the majority of problems related to EUS as a single imaging modality and related to the lack of deep vision during laparoscopy. The combination of EUS and LUS predicted R0 resection in 91% of the patients, thus significantly increasing the overall accuracy when compared to EUS alone. The prediction of R1/R2 resections showed similar results but with wide confidence intervals. Following EUS and LUS the number of futile laparotomies was reduced to 5%, and this figure dropped to 2.4% when patients who needed surgical by-pass were excluded.

LUS guided biopsy
After having developed and tested a new system for LUS guided fine-needle aspiration biopsy and tru-cut biopsy the author evaluated the need for biopsy using the same stringent indications as for EUS-FNA. LUS guided biopsies were indicated in 12% of the patients with a final malignant diagnosis. The major overall indication was lack of biopsy from the primary tumour. Adequate material was obtained in 95% of the biopsies despite being taken by six different surgeons. The overall combined impact of laparoscopic and LUS guided biopsy in patient management amounted to 27%.

Cost-effectiveness of different imaging strategies in the detection of patients with non-resectable disease
In a retrospective design monitoring the costs on a departmental level EUS and LUS – or a combination with either of these – was cost-effective regarding the detection of patients with non-resectable or disseminated disease. The combination of non-invasive methods (e.g. CT and EUS) seemed attractive from an economical view-point, but such a strategy would be associated with futile surgery in 20% of the patients. However, the combination of EUS and LUS almost eliminated futile laparotomies, and at the same time remained cost-effective. Although not reported the data proved resistant to significant changes in both costs and effect, and the sequential use of EUS followed by laparoscopy and LUS seemed to be a cost-effective strategy.

Combined pretherapeutic EUS and LUS as predictors of long term survival
The literature has suggested a correlation between specific pretherapeutic EUS findings and the prognosis in UGIC patients. Based on an improved evaluation by the combination of EUS and LUS it was relevant to relate the pretherapeutic findings of this strategy to the final prognosis, and to do a stratified analysis based on both the stage and the resectability assessment. The combined approach of EUS and LUS provided relevant and significant stratification estimates of the prognosis in all three cancer types whether based on stage or on resectability assessment.
A comparison of survival following R0 resection between patients selected by a CT based strategy and patients selected by the combination of EUS and LUS was not possible. In pancreas cancer, however, it was noted that despite similar R0 resection rates the patients selected by EUS and LUS seemed to have a better prognosis than reported in CT based studies. In the light of the ongoing discussion of "true" R0 resections in pancreas cancer EUS and LUS seemed superior to other imaging strategies regarding the identification of patients who may undergo a "true" R0 resection. Thus, EUS and LUS may have a positive impact on the prognosis of R0 resected UGIC patients.

Conclusion
The results from the author's ph.d. demonstrated the value of EUS as a single imaging modality, but it was also evident that this technology alone was unable to perform a complete pretherapeutic evaluation of UGIC patients.
With the results from the present thesis the author has defined and tested a new evaluation strategy based on the combination of EUS and LUS. This combination was supplemented by EUS and LUS guided biopsies in those situations, where a malignant biopsy would change the subsequent treatment strategy.
The combination of EUS and LUS was lenient, safe and cost-effective and at the same time provided additional, important pretherapeutic information regarding possible treatment options and the prognosis. It may be speculated if the improved patient selection has had a positive impact on the prognosis of the R0 resected patients.
The combined strategy may also allow a more homogenous selection of patients for future treatment trials.

Perspective
The author's work and the conclusions from this thesis have had a significant impact on the national strategy regarding the evaluation and treatment of UGIC patients. The combined evaluation strategy developed by the author has been recommended in the evidence based national clinical guidelines for UGIC patients (www.dpcg.dk, www.gicancer.dk), and the strategy is used in the national cancer packages ("Kræftpakker") which have been issued by the National Board of Health, Denmark (e.g. "Pakkeforløb for kræft i bugspytkirtlen 2009", www.sst.dk) and implemented by the Danish Regions.
Statutory national databases which are monitoring the quality of the evaluation and treatment of UGIC patients are supporting the authors combined evaluation strategy. A comparison between results from the author's institution with centres where a similar strategy has not been fully implemented yet shows, as an example, that the number of futile operations is significantly higher in the latter institution (www.dpcg.dk, www.gicancer.dk)(1, 146).
The combination of EUS and LUS is now used as standard in multidisciplinary, multi-centre cancer trials in order to obtain an optimal patient selection. A national study regarding downstaging of locally advanced pancreatic cancer is an example of a trial

which would have been impossible to perform without the use of this combination and the author's experience with its use(147).

8. FUTURE ASPECTS

However desirable it was not the primary goal or intention of the present work to improve the overall prognosis in UGIC patients. At this point the author has provided evidence as to the combined sequential use of EUS, EUS-FNA, LAP, LUS and LUS guided biopsy for an accurate and lenient stratification of UGIC patients into relevant and predefined treatment groups.

The multidisciplinary approach

The promising survival data after R0 resection(IX) were obtained prior to the introduction of neo-adjuvant and adjuvant therapy at the author's institution. Today the majority of UGIC patients receive some form of adjuvant therapy, and this will hopefully improve outcome in these patients. The multidisciplinary approach to UGIC has made substantial progress due to new treatment strategies and due to the improved ability to select patients based on EUS and LUS findings. The primary selection and the re-evaluation of patients with locally advanced pancreatic cancer for attempted downstaging by chemoradiation therapy is an excellent example(147). Addressing the issue of patient selection it is interesting that indirect signs of malignancy (e.g. EUS criteria, CT lymph node size, and PET positive findings) are still considered positive evidence of for example N1 and M1 disease. If clinical and/or study relevant then the detection of N1 or M1 disease should be documented by biopsy (e.g. EUS-FNA) and not by size and/or sonographic criteria alone. Thus, the future use of EUS and LUS in prospective, multidisciplinary clinical studies should include relevant biopsies as well.

Technical aspects

Technical improvements and new concepts emerge faster than ever in all areas of modern imaging. Unfortunately, it is impossible to perform relevant clinical testing at the same rate, and therefore many of the new features become commercially available without any documentation in terms of clinical use, impact or cost considerations.

Endoscopic sonoelastography has been introduced as a new EUS feature which may help discriminate between benign and malignant tissue(148). However, there are technical limitations, and the present goal is not to replace tissue confirmation, but to guide or minimize the number of nodes or tumours for EUS-FNA.

Contrast enhanced harmonic EUS has also been promoted on a potential ability to differentiate between benign and malignant tissue(149, 150). However, there are limitations resulting in artefacts and potential misinterpretation of the obtained images. A new prototype echoendoscope provides a potential solution to some of the technical problems and has enabled contrast enhanced harmonic EUS imaging with clear visualization of microvascular changes in lymph nodes and pancreatic lesions(151). The diagnostic and staging impact of contrast enhanced harmonic EUS are unknown, but technology seems to enhance minute EUS details in normal and malignant tissue, and this aspect could be of interest in monitoring treatment effects and in the EUS-FNA targeting.

Several studies have demonstrated the difficulties of a specific "Node-to-node" comparison between EUS, surgery and final histopathology. If the lymph node in question could be marked during the EUS or LUS procedure, and this marking could be detected during surgery, then there would be a topographical confirmation of the lymph node location as well as a 100% accurate "Node-to-node" comparison. Data on both aspects are lacking, but the author's group designed a EUS guided marking system where preliminary results provided evidence suggesting a solution to these problems(152). The potential clinical value of this technique may depend on the future use of neo-adjuvant therapy, extent of lymph node dissection as well as on the ability to perform EUS guided tumour therapy.

EUS guided tumour therapy has shown some potential which may become even more interesting with the development of new agents for direct tumour therapy as well as improved seeds for local brachytherapy. The ability of EUS to apply therapeutic agents directly into tumours and lymph nodes, which are otherwise inaccessible, is attractive from both an oncological and a patient related point of view. Preliminary data are interesting(153) including observations on patient safety, but more work has to be done regarding the delivery system and the development of locally active specific substances for tumour destruction. LUS guided therapy might also become interesting in connection with direct tumour therapy in locations outside the reach of the echoendoscope, and thus extending the scope for laparoscopically directed therapy.

PET-CT

Only combined imaging strategies seem relevant in the pre- and posttheraputic patient evaluation since no single imaging modality is capable of covering all aspects of modern cancer treatment. Some data suggest that PET-CT could provide a better pretherapeutic sensitivity regarding distant metastases(154) and PET-CT seems the best imaging modality to monitor the effect of neo-adjuvant therapy(155). Thus, the natural next step in UGIC imaging would be to include PET-CT in the combination of EUS and LUS, and to apply this approach to deal with the reported problems of false positive PET findings.

"Tissue is (still) the issue"

Since the test performance of an imaging based differentiation between benign and malignant lesions may never reach a 100% accuracy there will still be need for cytological or histological confirmation in selected clinical cases. The optimal technique of the EUS-FNA procedure itself as well as the EUS-FNA accessories may not experience any significant progress over the coming years, but the ability to provide a higher diagnostic accuracy on limited cell samples have improved using various new cytopathological analyses procedures. Immunohistochemical staining and even mutation analyses are now possible on EUS aspirated cells(22, 156) and this provides interesting aspects regarding micro metastases and differential diagnostic dilemmas.

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