Endoscopic ultrasound for staging of colonic cancer proximal to the rectum: A systematic review and meta-analysis

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ABSTRACT

Background and Objectives: Treatment of colonic cancer patients is highly dependent on the depth of tumor invasion (T-stage) as well as the extension of lymph node involvement (N-stage). We aimed to systematically review the accuracy of endoscopic ultrasound (EUS) for staging of colonic cancer proximal to the rectum. Patients and Methods: Men and women with colonic adenocarcinomas were included in the study. EUS staging was compared to histopathology as the gold standard. Outcome measures were T- and N-staging accuracies. Articles were searched in PubMed, Web of Science, The Cochrane Library, and EMBASE. Results: Six studies were identified comparing EUS staging of colonic cancer to histopathology. The pooled-staging sensitivity and specificity were 0.90 and 0.98 for T1 tumors, 0.67 and 0.96 for T2 tumors, and 0.97 and 0.83 for T3/T4 tumors, respectively. Sensitivity and specificity for N+ disease were 0.59 and 0.78, respectively. Conclusions: EUS is a feasible method for T-staging of cancers of the colon proximal to the rectum. The accuracy of lymph node staging needs to be verified by prospective multicenter studies including larger patient populations.

Key words: Colonic cancer, endoscopic ultrasound, staging, systematic review

INTRODUCTION

Colorectal carcinoma represents a global health burden as the most common cancer of the digestive tract. It is the third most frequent cancer diagnosed in males and the second in females.[1] Preoperative status of tumor invasion depth is important for the selection of endoscopic treatment or surgical resection. In addition, stratification based on stage is also important for selecting patients to the established neoadjuvant radiochemotherapy for rectal cancer and promising neoadjuvant chemotherapy for patients with colon cancer.[2] In rectal cancer, transluminal endoscopic microsurgery has shown to be an effective and...
safe procedure for selected patients. The value of transrectal ultrasound (TRUS) for the staging of rectal cancer has been investigated in numerous studies. Thus, TRUS has become the method of choice for locoregional T-staging of rectal cancer while N-staging needs further refinement in diagnostic criteria and endoscopic ultrasound (EUS) technology to improve diagnostic accuracy. Only limited literature exists concerning colonic neoplasms.

In this systematic review, we aimed to systematically review the literature assessing the value of EUS-based staging of malignant colonic neoplasms compared to histological stage.

**PATIENTS AND METHODS**

The review was conducted according to the PRISMA guidelines (PROSPERO registration number: CRD42015016013). Literature search was performed in June 2015 in PubMed (1946–2015), EMBASE (1980–2015), Web of Science (1900–2015), and The Cochrane Library (1972–2015) [Figure 1]. A search was performed using the following MeSH terms: [colon cancer], [colonic neoplasms], [colon neoplasms], [colonic cancer] and [endoscopic ultrasound], [ultrasonography] using the Boolean operators OR/AND. Two authors individually assessed all abstracts found in the primary search (MLM, IG). English, German, and French studies were evaluated. A “snowball” search was manually performed from the reference lists of included studies. Finally, all included studies were crosschecked in Web of Science under “citations.”

Data regarding study characteristics, diagnostic methods, and accuracies of T- and N-stages with histology as controls were extracted. Studies with combined accuracies for rectum and colon were only included if the colonic data could be separated from the rectum data. Authors of studies with mixed data where separation was not obvious were contacted. For each separate study, characteristics such as demography, study design, inclusion and exclusion criteria, patient numbers, sample size calculations, and endpoints were evaluated and are presented in Table 1. Data on endoscopic equipment, operator experience, blinding, measure categorization, adverse events, missing data, and treatment and comparisons to other diagnostic modalities are presented in Table 2. Studied data are referred to without interpretation.

There is no consensus on the assessment of the quality of clinical studies lacking a control arm; however, we chose to include studies based on inclusion criteria and completeness of data as well as to assess the risk of bias in each individual study. The guidelines from the (STARD) The Standards for Reporting of Diagnostic Accuracy

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Figure 1. Flowchart on the search strategy
Table 1. Schematic setup summarizing the study characteristics and design including inclusion and exclusion criteria, demography, number of patients, sample size, and endpoints for the different studies

| Study | Demography | Design | Inclusion criteria | Exclusion criteria | Patients, n | Sample size | Endpoints |
|-------|------------|--------|-------------------|-------------------|-------------|-------------|-----------|
| Stergiou | Men and women | Prospective trial | Patients awaiting laparoscopic or endoscopic resection of colonic cancer | Locally advanced tumors or systemic spread of tumor | 33 | Not described | Diagnostic accuracy, T-and N-stage |
| Kuntz | Men and women, ulcerative colitis + familiar polyposis overrepresented | Prospective trial | EUS performed in patients where it was expected that there would be therapeutic implications. Inclusion from February 1995 to December 1996 | Not fulfilling the inclusion criteria | 23 | Not described | Diagnostic accuracy, T- and N-stage |
| Kongam | Men (11), women (10) | A retrospective study with prospectively entered database | Patients aged 18-80, with colonic cancer and endoscopic or surgical resection within 4 weeks. Inclusion from March 2012 to February 2013 | Contraindications for surgery or EUS examination | 21 | Not described | Diagnostic accuracy, T- and N-stage |
| Lok Tio | Men (17), women (13) | Prospective trial | EUS performed 1-4 weeks prior to colonic cancer surgery. Inclusion from March 1984 to October 1989 | Not fulfilling the inclusion criteria | 30 | Not described | Diagnostic accuracy, T- and N-stage |
| Tseng | Men and women | Prospective trial | Patients with biopsy-proven colorectal carcinoma | Not fulfilling the inclusion criteria | 29 | Not described | Diagnostic accuracy, T- and N-stage |
| Haji | Men and women | Prospective trial | Patients listed for surgical resection of a colon cancer. Inclusion from March 2008 to April 2009 | Not fulfilling the inclusion criteria | 38 | Not described | Diagnostic accuracy, T- and N-stage with EUS and CT |

EUS: Endoscopic ultrasound, CT: Computed tomography

initiative have been used to evaluate the completeness of reporting in studies on diagnostic accuracy [Tables 1 and 2], as well as to assess bias.[9]

Statistical analysis

Pooled estimates of sensitivity and specificity were calculated using the Rutter and Gatsonis Hierarchical Summary Receiver Operating Characteristic (HSROC) model.[10,11] Possibly due to the limited number of studies and high proportions of studies having a specificity at 1 for the T2 tumors, the random effect model failed to fit. Assumptions for using the Rutter and Gatsonis HSROC model might be violated as the T2s have two thresholds, both toward T3 and T1. In this case, a fixed effect model was used for estimating sensitivity and specificity. Sensitivity and specificity were given with a 95% confidence interval (CI).

Data were entered in RevMan 5.3 (Review Manager Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and used for drawing the figures. Calculations of pooled sensitivity and specificity were performed using the SAS macro MetaDas 1.3 (User Guide Version 1.3. 2010 July; available from: http://srdta.cochrane.org/ref) on SAS version 9.4 (SAS Institute Inc., 2012, Cary, NC, USA).

RESULTS

The initial search proposed 747 articles, with 58 excluded as duplicates, 638 irrelevant records, and 51 assessed for full-text eligibility. Of these, only six were relevant.[12-17] A flow chart of the search strategy is presented in Figure 1. Six potential studies were excluded from the study due to data on colonic cancers alone could not be provided. One author provided separate tumor node metastasis classified data for colonic tumors but only included adenomas and very early cancers and was excluded from this review.[18] Other authors of mixed data studies were unable to provide information on colon cancer patients alone or did not reply. The latter studies were excluded from the review.

The total number of patients with colonic cancers evaluated for T-stage with EUS and with surgical pathology at the gold standard was 208. The study by Haji et al. counted as two studies due to the same patient population was evaluated with two ultrasound frequencies with each set of data calculated separately.[17] None of the studies reported any complication due to the diagnostic procedures either with miniprobes[12,16,17]
or with radial transducers. Some, however, had to give up tumor staging due to technical difficulties; these were not included in our analysis.

In terms of N-stage, most studies evaluated this parameter based on histology of the surgical resection specimen after laparoscopy or open surgery. Two studies adjusted for local resections.

The T- and N-stages from the six analyzed studies were as follows:

- T1: A summary of the studies for patients with T1 disease is shown in Figure 2a. The pooled sensitivity was 0.90 (95% CI: 0.66–0.98) and the specificity was 0.98 (95% CI: 0.94–0.99).
- T2: A summary of the studies for patients with T2 disease is shown in Figure 2b. The pooled sensitivity and specificity were calculated using a simple fixed effect model. The pooled sensitivity was 0.67 (95% CI: 0.50–0.80) and the specificity was 0.96 (95% CI: 0.92–0.98).
- T3/T4: A summary of the studies for patients with T3/T4 disease is shown in Figure 2c. The pooled sensitivity was 0.97 (95% CI: 0.88–0.99) and the specificity was 0.83 (95% CI: 0.73–0.90).
- N: A summary of the studies for patients with
Figure 2. Forest plot with a cross table on included patients for diagnostic accuracy measurements for endoscopic ultrasound in comparison to histology for (a) T1, (b) T2, (c) T3/4, and (d) lymph node positive patients. Sensitivity and specificity with 95% confidence intervals have been given in numbers as well as illustrated graphically

N-positive disease is shown in Figure 2d. The pooled sensitivity was 0.59 (95% CI: 0.31–0.82) and the specificity was 0.78 (95% CI: 0.68–0.86).

DISCUSSION

The aim of this systematic review was to assess the diagnostic accuracy of EUS for staging of malignant colonic tumors proximal to the rectum. Six studies, evaluating 208 patients with colonic cancer, in terms of tumor stage compared to pathological stage, were identified and sensitivity and specificity on T- and N-stages were calculated. T-staging with EUS of colonic and rectal tumors can be compared in terms of accuracies.

For rectal tumors, EUS in early tumors (T1/2) has been considered the staging modality of choice.

At present, the image modality of choice for staging of colonic cancer is a CT-scan. The study by Haji et al. is a comparative study between the image modalities of CT and miniprobe EUS. The EUS was found to be significantly more accurate in the local staging of both early and advanced tumors.[17] There is an ongoing prospective, randomized trial,[2] evaluating neoadjuvant chemotherapy in locally advanced operable T3/T4 colonic tumors. Neoadjuvant therapy may target micrometastatic disease earlier, downstage tumor, as well as reduce surgical tumor cell shedding.[22] If operable, T3/T4 cancers will benefit from neoadjuvant therapy. The accuracy of staging will become even more important, allowing quicker assignment to correct multimodal treatment.

The results of this review have to be interpreted in the context of limitations of the calculations and the risk of bias in the systematic review and its sources. Tables 1 and 2 illustrate some heterogeneity in study designs: The resection methods as well as the operator dependency using the EUS technique. Only a few of the studies mention blinding concerning pathologists and endoscopists,[14,17] which may potentially lead to differentiated and nondifferentiated informational bias. Selection bias undoubtedly occurs since some studies include highly selected patients.[12,13] None of the studies described power calculations made prior
Comparing different types of endoscopes and frequencies could also affect the results. It is argued that staging by miniprobe is advantageous in staging of stenotic tumors because the miniprobe, which is passed through the biopsy channel of an ordinary colonoscope, is highly successful in passing stenotic lesions in contrast to conventional EUS endoscopes. Some studies emphasize that miniprobes are also useful for staging of small and flat lesions. Miniprobes however using high ultrasonic frequency with low penetration depth will not be able to examine all layers of the colonic wall or lymph nodes. This is especially true for advanced cancers that infiltrate deeper layers. Conventional EUS may pose difficulties in obtaining cross-sectional images over lesions located over a colonic bend or in strictures. Others argue that a radial echoendoscope can be considered a feasible staging instrument for colonic cancers in all sections of the colon. Authors state following reasons for staging inaccuracy: (1) presence of inflammation in the subserosal layer as a reason for overstaging T1 to T2 and (2) understaging of T2 and T3 tumors primarily due to difficulties in distinguishing carcinomatous microinfiltration from inflammatory changes. Overall, only very few T4 tumors were evaluated. This may be due to the fact that T4 tumors have a high risk of stenosis and are therefore difficult to evaluate by EUS.

EUS in general is a standard procedure for staging of many gastrointestinal lesions and an EUS examination of the entire colon has been shown to be technically feasible and safe. Due to the colorectal screening programs, an increasing number of tumors of the colon is found at earlier stages. This fact, combined with a population of increasing age with higher risks of comorbidity, puts clinicians in therapeutic dilemmas. For elderly comorbid patients who are questionable candidates for major surgery, EUS could possibly open a new avenue for treatment decisions such as small local tumor resections, or in the near future, full-thickness endoscopic resection as a routine procedure based on T-staging evaluation with exclusion of local lymph node metastases. The latter evaluation is a challenge at present as N-staging significantly impacts colonic cancer management and imaging methods used today are inaccurate. Further studies should be undertaken in the future with larger numbers of patients to clarify whether EUS will prove useful for staging of cancer of the colon.

Apart from therapeutic stratification to neoadjuvant chemoradiation, preoperative TN-staging of colorectal cancers is also of importance for prognostication. Consequently, there is also present interest in other imaging methods to additionally subclassify these cancers. Evaluation of tumor vascularity by EUS is such a method that may be useful both for prognostication and for assessment of the efficacy of antiangiogenic agents early in the course of therapy. Imaging and evaluation of the blood flow velocity and direction can be carried out using Doppler sonography. The feasibility of contrast-enhanced EUS (CE-EUS) examinations with second-generation microbubble contrast agents used as Doppler signal enhancers was proven by several groups. Evaluation of tumor perfusion can also be performed by low mechanical CE-EUS. According to the European Federation Societies in Ultrasound in Medicine and Biology guidelines, CE-EUS can be utilized to assess early response to biologic therapy in tumors, such as metastatic gastrointestinal stromal tumor, renal cell carcinoma, and hepatocellular carcinoma. A similar approach has recently been described for quantitative assessment of tumor perfusion in colorectal cancer.

Very few studies have evaluated the use of EUS for staging of malignant colonic neoplasms. Accurate staging of colonic cancer proximal to the rectum is becoming increasingly important for treatment decisions in the setting of modern oncology and technical advancements in surgery and endoscopy. EUS may become an important imaging modality in the determination of the therapeutic approach to patients with colon cancer; however, further large multicenter trials are necessary before firm conclusions can be drawn, especially regarding evaluation of the N-stage.

**CONCLUSION**

Very few studies have evaluated the use of EUS for staging of malignant colonic neoplasms. Accurate staging of colonic cancer proximal to the rectum is becoming increasingly important for treatment decisions.
in the setting of modern oncology and technical advancements in surgery and endoscopy. In this study we found the pooled-staging sensitivity and specificity to be 0.90 and 0.98 for T1 tumors, 0.67 and 0.96 for T2 tumors, and 0.97 and 0.83 for T3/T4 tumors, respectively. Concerning N+ disease, the sensitivity and specificity was 0.59 and 0.78, respectively. EUS may become an important imaging modality in the determination of the therapeutic approach to patients with colon cancer; however, further large multicenter trials are necessary before firm conclusions can be drawn, especially regarding evaluation of the N-stage.

Acknowledgments
We thank Janne Wendt Librarian at Herlev Hospital for her help in relation to literature search.

Financial support and sponsorship
The study was partially funded by Agnes and Poul Friis Fund, Astrid Thaysens Legat, Axel Muusfeldts Fund, Dansk Medicinsk Selskab, Krista and Viggo Petersens Fund, Arvid Nilssons Fund, Director Jacob Madsens and wife Olga Madsens Fund, Director Svend Espersens Fund, Lykkefelds Fund, and the Research Councils of Herlev and Koge Hospitals.

Conflicts of interest
There are no conflicts of interest.

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