Surgery for colorectal cancer: improving staging by the sentinel lymph node procedure
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General introduction
and outline of this thesis
Colorectal cancer

Epidemiology

In the Netherlands colorectal cancer (CRC) is the second most common type of cancer with more than 12,000 new patients in 2009. In 2008 approximately 4800 patients deceased from the effects of colorectal cancer, making it the second leading cause of death from cancer in the Netherlands after lung cancer. The incidence of colorectal cancer increases with one percent each year. In 2010 the Health Council of the Netherlands advised to start a screening program for colorectal cancer. If this program will start a further increase in incidence can be expected. Therefore colorectal cancer will remain a major health problem and all efforts must be made to optimize treatment strategy and increase survival of these patients.

Surgical treatment

The initial treatment for patients with nonmetastatic CRC is surgical resection. In 2010 more than 8100 resection for primary CRC were performed in the Netherlands. The resection can either be performed via an open or laparoscopic approach. Over the years the number of laparoscopic resections increase: in 2010, 42% of the elective resections were laparoscopically performed. During surgery a complete resection of the primary tumor with en-bloc resection of the regional lymph node bearing the mesentery should be performed. The role of regional lymphadenectomy in CRC is well established: it involves local-regional control, cancer staging, adjuvant treatment planning, and it affects overall survival. Nodal involvement is the most important prognostic parameter, and is the pillar in consensus-driven treatment decision-making for adjuvant chemotherapy. The American Joint Committee on Cancer (AJCC) recommends at least 12 harvested lymph nodes per resection specimen for accurate nodal staging, but in daily clinical practice the nodal yield varies with over 50% of resection specimens containing fewer than 12 lymph nodes. In the Netherlands 22% of the resection specimens contained less than ten lymph nodes. This relates to a clinically significant understaging in CRC.

Complete resection of early stage CRC without involvement of lymph node metastases should cure the patient. However, up to 30% of the patients with early node-negative CRC will have recurrent or metastatic disease following potentially curative resection. Apart from incomplete surgical resection, inadequate staging of CRC may be caused by insufficient pathologic regional nodal retrieval, sampling error or overlooked small volume nodal metastasis by conventional methods. Serial sectioning and additional immunohistochemical analyses or reverse transcriptase-polymerase chain reaction (RT-PCR) could diagnose lymphatic spread more accurately. Ideally, all regional lymph nodes should be examined with these
techniques for occult tumour cells (OTC), but this would be too expensive and
time-consuming and therefore not feasible in everyday practice.

Sentinel node procedure

The sentinel-lymph-node concept (SN) could offer a solution.10 This concept is based
on the stepwise lymphatic spread. The sentinel node procedure identifies lymph
nodes most likely to harbour metastases. During the sentinel node procedure patent
blue is injected around the tumour for lymph mapping. In this way lymphatic flow to
the first blue lymph nodes can be visualised. These lymph nodes are identified as
sentinel nodes. (Figure 1) This facilitates the pathologist to study only the few SNs
removed in greater detail for tumour burden, compared to the conventional
Haematoxyline and Eosin (H&E) staining of all lymph nodes which is currently done in
routine daily practice. The SN procedure could refine staging, thereby identifying a
patient group with tumour cells in the resected lymph nodes which is overlooked by
conventional analysis. Potentially these patients have a higher risk for tumour
recurrence or metastatic disease and therefore might benefit from adjuvant chemotherapy.

In breast cancer and melanoma, the SN procedure is an important step in
treatment strategy.11,12 If detailed analysis of the sentinel lymph node reveals no
metastasis the lymphadenectomy will not be performed. In contrast to breast cancer
and melanoma, regional lymphadenectomy is an integral part of the surgical
procedure in CRC. Therefore, SN biopsy in CRC is only an adjunct potentially improving
staging without clearly defined prognostic impact and therapeutic implications so
far. Numerous, generally small and single-institution, studies assessed the feasibility
of SN with varying conclusions. The SN procedure for CRC has not been standardised,
and the methods, materials, and patient selection vary by institution and surgeon.13-36

Outline of this thesis

In this thesis the role of the sentinel lymph node procedure in CRC surgery is
described. The aim of our research is to assess the accuracy of SN-mapping in staging
patients with CRC. In Chapter 1 we performed a systematic review to determine the
diagnostic accuracy of this procedure from published data and to identify factors
that contribute to the conflicting reports. In Chapter 2 we made a prospective
comparison between colon and rectal cancer to analyse whether differences in
anatomy and pre-operative treatment of rectal cancer affect the predictive value
of the SN procedure. In addition, the incidence of micrometastatic disease in
histologically negative lymph nodes was assessed, and the ability to refine staging by
additional immunohistochemical analysis compared to conventional histopathological
examination. However, in the literature additional analysis is limited to the SN only.
In Chapter 3 we analysed the real diagnostic accuracy of the SN procedure in
upstaging patients. Therefore the incidence of OTC in SNs was compared to the
presence of these cells in all histologically negative lymph nodes of these patients
and related to clinical pathological characteristics. Also, three different antibodies used for
the immunohistochemical analysis were compared to determine the sensitivity and
specificity of these antibodies.

The detected OTC are analysed and classified by the pathologist. This classification
can be performed using the International Union Against Cancer (UICC) TNM-
classification with both quantitative and qualitative criteria. According to this
definition OTC are isolated tumour cells without clinical consequence if they are
smaller than 0.2mm, or show no sign of activity (no proliferation, no desmoplastic
stroma-reaction) and are localised in the lymphatic sinus. On the other hand if isolated
tumour cells are detected at the parenchyma of the lymph node, they are considered
micrometastases (pN1mi+). However, in the 6th edition of the American Joint
Committee on Cancer (AJCC) TNM-classification only quantitative criteria are used.
Therefore, in Chapter 4, we examined the interobserver variability among pathologists
in classifying OTC in lymph nodes in CRC.

Isolated tumour cells smaller than 0.2 mm are supposed to be of no clinical relevance.
These cells have a limited life-span and levels of circulating tumour cells can be
demonstrated in peripheral and portal blood during intra-operative manipulation of
colorectal tumours. During a laparoscopic resection the tumour is not manipulated

Figure 1 Blue sentinel lymph node
using the no-touch isolation technique. It can be hypothesised that during a laparoscopic resection less OTC are distributed into the lymphatic flow passing the lymphatic sinus. In Chapter 5 we assessed the effect of the surgical approach (i.e. open lateral to medial versus laparoscopic no touch medial to lateral approach) on the levels of OTC in sentinel lymph nodes of patients with early stage I and II CRC.

Although upstaging of colorectal patient with SN procedure has been described, the clinical impact of these findings remains controversial because survival analyses of these patients are lacking. In Chapter 6 we describe our prospective analysis of the effect of SN mapping, in patients with CRC, on nodal staging and its prognostic impact in terms of disease recurrence and survival. During the SN procedure patent blue is injected around the tumour for lymph mapping. In pre-operative work up for CRC colonoscopic tattooing with Indian ink is performed to mark the tumour site before surgery. Colonoscopic tattooing is necessary to localise the tumour during surgery, particularly in laparoscopic resection where palpation of the tumour is not possible. Finally, in Chapter 7 we compared colonoscopic tattooing to the SN procedure and analysed if it can contribute to staging accuracy by analysing whether it leads to a higher lymph node yield per specimen, and to determine its diagnostic accuracy.

References