Lymph node staging in colon cancer

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Chapter 1

Introduction, aim and outline of the thesis

Introduction

Adequate surgical resection including en-bloc removal of the involved colon segment and associated mesenteric lymph nodes as well as accurate pathological examination of resected lymph nodes are prerequisites for accurate tumor staging in colon cancer. Staging of patients based on the pathological tumor, node, metastasis (pTNM) classification system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), is important for both selection of patients for adjuvant treatment and prediction of long-term survival.[1] The single most important determinant of prognosis in patients with localized colon cancer is the presence of nodal metastases at the time of surgical treatment. The 5-year survival rate is 70-80% for patients with node negative disease (stage I/II), but only 45-50 % for those with node positive tumors (stage III).[2] In patients with stage III colon cancer adjuvant chemotherapy improves survival considerably.[3-5] In addition, a recent meta-analysis showed that there might be a benefit of adjuvant treatment in high-risk stage II colon cancer patients.[6] Therefore, it is highly important to accurately reflect the status of the regional lymph nodes.

The fact that about 20% of the patients without lymph node metastases develop recurrent disease after apparently curative surgery, leads to the question if there might have been understaging at the time of the primary operation.[7] It is possible that in this group of patients small lymph node metastases have been missed. This may be due to an inadequate surgical lymphadenectomy or inadequate pathological examination.[8] According to international guidelines meticulous pathological examination of at least 12 lymph nodes is warranted for adequate staging of patients with colon carcinoma.[1] However, several studies showed that the minimal number of lymph nodes necessary for correct staging varied considerably from 6 to 18 to as many as possible in the study of Goldstein et al.[8-12]

In depth pathological examination of lymph nodes by immunohistochemical staining for cytokeratin or reverse transcriptase-polymerase chain reaction (RT-PCR) may reveal micrometastases that could have been missed by routine haematoxylin & eosin (H&E) examination. There have been conflicting results on the impact of micrometastases and/or tumor DNA in mesenteric lymph nodes on survival.[13,14] [15,16] [17-20] Several authors have reported a decreased survival rate when micrometastases are detected in colon carcinoma.[13,14] [15,16] The possible benefit of adjuvant therapy in this group of patients is therefore not clear yet.

Ultrastaging techniques are time consuming, labour intensive and costly. For optimal staging, in depth examination of only the sentinel lymph node (SLN) could be helpful. The technique of the sentinel node biopsy was first described and performed by Cabanas (1977) in penile carcinoma.[21] Morton et al. and Giuliano et al. introduced the sentinel node biopsy for staging patients in general practice in melanoma and breast cancer.[22,23] In colon cancer, the SLN's are defined as the first one to four blue-stained nodes with the most direct lymph drainage from the primary tumor.[24] They are the most likely to harbor metastatic disease when present, enabling focused examination with multilevel microsectioning of the SLN's to provide a more efficient and cost-effective detection of micrometastases. In addition, patterns of aberrant lymphatic drainage can be visualized with sentinel lymph node mapping, which may lead to a more extended resection.[25]

Aim and outline of this thesis

Main goal of this thesis is to investigate the current problems with lymph node staging in colon cancer and to describe possible improvements in lymph node sampling in order to make a better selection of patients eligible for adjuvant treatment.

Chapter 2 starts with a population based study in which the impact of the number of examined lymph nodes in colon cancer on survival is studied. In addition, the tumor and patient factors important for the number of harvested lymph nodes were examined.

In **Chapter 3**, the effect of lymph node fixation with modified Davidson's fixative (mDF) on the number of examined nodes and lymph node status is described.

Chapter 4, 5 and 6 describe the sentinel node procedure in colon cancer. Chapter 4 presents a pilot study on the feasibility of the procedure for patients with localized colon cancer. In chapter 5, we studied the accuracy of the SLN procedure in a multi-centre setting with a special focus on nodal upstaging and aberrant lymphatic drainage. Chapter 6 deals with validation of the procedure, tested with RT-PCR examination of all tumour negative lymph nodes. The main goal of this part of the study is to validate a method in which it would be sufficient to examine only the SLN's with ultrastaging methods in stead of all H&E negative lymph nodes.

In **Chapter 7**, a review is presented in which an overview of the history of adjuvant chemotherapy in colon cancer is given with a special attention to the effects of chemotherapy in high risk stage II patients.

The discussion of the aforementioned studies as well as future perspectives are presented in **Chapter 8** , while **Chapter 9** contains a Dutch summary.

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