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Lymph node staging in colon cancer

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Chapter 8

Summary, Conclusions and Future Perspectives

Summary

The prognosis of patients with colon cancer is generally related to the degree of invasion of the tumor through the bowel wall and the presence or absence of lymph node involvement and distant metastases. Adjuvant chemotherapy is given to patients with lymph node metastases (stage III) and some patients without nodal metastases but with certain unfavorable tumour characteristics. Despite the good prognosis of patients without lymph node metastases (stage II colon cancer), 20-30% of these patients will develop recurrent disease, even after apparently curative resection.[1]

In this thesis an attempt was made to improve current staging and to identify those patients in the current stage II group who have an increased risk of developing recurrent disease in the future and who might benefit from adjuvant treatment. This was based on the assumption that some patients in the stage II group actually belong to the stage III groep (patients with lymph node metastases). In other words, with the current techniques of lymph node analysis some nodal metastases may be missed, leading to a false node-negative classification in some stage II patients. There are two explanations for this nodal 'understaging'. It is possible that not enough nodes are identified from the colon specimen, leaving some positive nodes unidentified. In addition, it might be that the identified nodes are insufficiently examined, thereby missing the smaller metastases. Both hypotheses are examined in this thesis.

Chapter 2 starts with an evaluation of the quality of lymph node sampling in colon carcinoma in the Northern part of the Netherlands. The main goal was to study the impact of the reported number of lymph nodes at pathological examination on survival. Data of 2,281 patients with localized colon cancer were analyzed for factors associated with the number of examined lymph nodes. The effect of tumor characteristics and examined lymph node numbers on nodal status and survival were analyzed. From these data we can conclude that in the majority of cases less than the recommended number of twelve nodes in the guideline are examined.[2] T-stage, tumor localization and patient age were related to the number of nodes examined. A higher number of examined nodes was associated with an increase in node-positivity. The survival benefit with more examined lymph nodes in N_0 patients can be explained by stage migration. This means that with a higher number of examined nodes, more metastases are found, leading to less patients with occult nodal metastases who are unjustly assigned to the stage II group. These patients now belong to the stage II group, where they are a subgroup with a relatively good prognosis. This stage

migration may eventually lead to a survival benefit, as more patients will receive adjuvant therapy when more lymph node metastases can be detected. In **chapter 3**, we evaluated the effect of a different fixation method (modified Davidson's Fixative (mDF)) on the number of lymph nodes examined and staging in patients with colon carcinoma. Traditional formalin preparation with manual dissection of all nodes was performed in 117 colon specimens, while the specimens of 125 patients were fixated in mDF. Differences in the retrieval and number of nodes and size of suspected nodal metastases were measured. All lymph nodes were stained with conventional H&E methods. With the mDF technique the median number of examined nodes increases from five to thirteen. Smaller nodes and more micrometastases (6% vs 16%) were found. The percentage of node positive patients increased from 30 to 41%, leading to more patients being eligible for adjuvant chemotherapy.

In the next 3 chapters we report on the results of the sentinel lymph node biopsy (SLN) in colon carcinoma. In **chapter 4**, a short pilot study of 30 patients is described in which the feasibility of in vivo SLN detection with Patent Blue V dye is tested. In addition, we evaluated nodal microstaging and ultrastaging using cytokeratin immunohistochemistry (IHC) and reverse transcriptase-polymerase chain reaction (RT-PCR) methods. Subserosal injection with Patent Blue dye was used. In searching for occult micrometastases each SLN was examined at three levels. In tumor-negative SLN's at routine haematoxylin-eosin (H&E), IHC analyses and RT-PCR were performed. The procedure was successful in 29 out of 30 patients (97%). Upstaging occurred in 10 patients (33%); 7 by IHC and 3 by RT-PCR. Aberrant lymphatic drainage was seen in 3 patients (10%). From this pilot study, we conclude that the SLN concept in colon carcinoma using Patent Blue V is feasible and accurate. It leads to an upstaging of nodal status in 33 % of patients when IHC and PCR techniques are combined. The results of this study were confirmed in a larger multi-center setting in **chapter 5**. Without RT-PCR, we found 18% upstaging. It might be that these patients belong to the high risk stage II patients that we are looking for in our selection of patients for adjuvant therapy. However, long follow up results of these patients have to be awaited in order to interpretate the real significance of this upstaging. In addition to this upstaging, the SLN procedure might be helpful in selecting the right nodes that should to be examined in any case by the pathologist. With this procedure, small, blue sentinel lymph nodes might be detected that would have been missed with routine pathological analysis. In **chapter 6** we examined the validity of the SLN concept by performing reverse transcriptase-polymerase chain reaction (RT-PCR) with carcino-embryonic antigen (CEA) on tumor negative SLN's as well as non-SLN's. In nine colon tumors, H&E and IHC negative

SLN's were also negative with CEA-RT-PCR. A total of 105 lymph nodes, including 83 non-SLN's were retrieved in these nine specimens and none of the non-SLN's were CEA-RT-PCR positive. From these data we conclude that in this study, all tumor-negative SLN's correctly represent the tumor-negative status of the non SLN's in primary colon tumors. The reliability of this method in colon cancer seems promising.

In **Chapter 7,** the results of a review on adjuvant chemotherapy in colon carcinoma are presented, with a special focus on chemotherapy in high risk stage II patients. Since the late eighties and early nineties, 5-fluorouracil (5-FU) based chemotherapy is the standard adjuvant treatment for stage III colon cancer. In stage II patients, the role of adjuvant chemotherapy is still debatable. However, there is indirect evidence of benefit for patients with high-risk stage II disease including bowel obstruction, perforation, T4 stage and identification of less than 12 examined lymph nodes in the pathology report.

Conclusion and future perspectives

In this thesis we present some tools that might be used for the improvement in the nodal staging of colon cancer and thereby the selection of patients eligible for adjuvant chemotherapy. This can be accomplished by the examination of more lymph nodes and a better selection of these nodes, or by the use of more sensitive techniques in the detection of metastases. Both possibilities are outlined separately in the following paragraphs. In addition, alternative options for improvement in staging are discussed.

Although the international guidelines warrant examination of at least 12 nodes for adequate staging and treatment of patients with colon cancer, a retrieval of more nodes might be better.[2] With a fat-clearance technique a mean number of 50 lymph nodes per specimen can be found.[3] More than 70% of the metastatic lymph nodes were smaller than 5 mm in diameter and more than 30 lymph nodes were needed to achieve a 85% probability of true N0 status at standard histology.[3,4] Based on the above, we can readily assume that the pathologist only samples a small part of the regional lymph nodes, even when the minimum number of twelve nodes is examined. The chances of missing some lymph node metastases seem considerable, especially when we take into account that in a considerable amount of patients less than twelve nodes are examined as shown in this and other studies.[5] This assumption is supported by our finding of stage migration with more lymph nodes examined, as shown in chapter 2. Several studies have tried to find a cut off point for the minimal number of lymph nodes necessary for correct staging. This number varied considerably from 6 to 18 to as many as possible in the study of Goldstein et al.[3,6-9] Based on these studies and our study, it is not possible to make an evidence based statement on the amount of lymph nodes to be examined. Until there is evicence, the effort should indeed be to examine as much nodes as possible.

Next to the assumption that 'more is better' in lymph node staging, there is also the option of a more intensive pathological examination of the detected lymph nodes, as described in the introduction. Several authors have reported a decreased survival rate when nodal micrometastases are detected in CRC.[10-12] Liefers et al found a clear distinction in 5-year disease free survival in a group of stage II patients, based on the presence or absence of tumor RNA in lymph nodes.[12]

These intensive staging techniques are time consuming, labor intensive and costly. The technique with mDF as described in chapter 3 is a cheap and simple alternative to increase the number of nodes. As shown in our study in the chapters 4-6 in which the SLN procedure

was validated with RT-PCR examination of sentinel and non-sentinel lymph nodes, the SLN concept showed to be reliable in predicting micrometastases and/or isolated tumor cells or tumor RNA also in non-SLN's. This is confirmed with IHC in two other studies.[13,14] It seems sufficient to perform ultrastaging only on the SLN, while examining the non-SLN with H&E, which will save time and money. As shown in our data and other studies, the sentinel node procedure reveals aberrant lymphatic drainage in 2-9% of the cases.[15-17] Aberrant lymphatic drainage might be especially interesting in tumors situated at the rectosigmoid junction, as these tumors might behave either as sigmoid tumors or as rectal tumors. We will start a study on lymphatic mapping in these tumors in the near future.

As the ultimate goal is to improve the survival in patients with colon cancer, we have to consider whether it might be possible to improve the surgical technique, next to the pathological technique. From the introduction of the total mesorectal excision (TME) in rectal cancer it is known, that adequate resection of an intact rectal specimen leads to a better patient survival compared to survival when the specimen has been damaged during surgery.[18] In addition, it is known that the long-term survival following colorectal cancer surgery in general, improves significantly with increasing hospital caseload and surgeon's education.[19-21] Next to the harvest of a sufficient number of mesenteric lymph nodes, a diligent operative technique is probably essential to prevent intra-abdominal spill of tumor cells through manipulation of the tumor. Here the 'no-touch' technique seems important. It involves early ligation (before mobilization) of the feeding artery and central vein before manipulation of the tumor and associated mesentery. An important part of the no-touch principle is the preparation in existing anatomical plains and the avoidance of manipulation of the tumor and disruption of lymphatic channels. The early ligation of vessels at the base of the mesentery forces to perform an adequate dissection of the mesentery with the harvest of a sufficient number of lymph nodes in it. Turnbull et al found an increase in disease-free survival after the introduction of this technique.[22] In a prospective study no significant survival benefit of this technique was shown, although it did show a decreased incidence of liver metastases.[23] Although it is not clear which factor in the surgical technique is most important for survival, we should certainly not neglect the surgeon's effect on prognosis in colon cancer. We recently started a study to analyze the influence of the individual surgeon and pathologist on the number of examined lymph nodes and survival.

Regarding lymph node staging, it may be possible to improve the pre-operative knowledge of the tumor status by the use of new imaging techniques in the near future. In rectal

cancer, magnetic resonance imaging (MRI) is the gold standard for optimal pre-operative imaging of the distance of the tumor to the mesorectal fascia. It can predict the circumferential resection margin with a high accuracy and consistency, allowing preoperative identification of patients with a small margin to the fascia who have an risk of recurrence. These patients will benefit from preoperative chemo- and/or radiotherapy.[24] Until recently, there was no accepted, ideal imaging modality or technique for diagnosis of lymph node metastases. However, in the last few years, MRI with ultra small super paramagnetic iron-oxide nanoparticle (USPIO) as a contrast agent is used for diagnosis of lymph node metastases. It offers higher diagnostic precision than unenhanced MRI for detection of lymph node metastases, and allows functional and anatomical definition when used as an imaging modality.[25] USPIO-MRI has been tested in several solid cancers and seems useful in identifying benign and malignant lymph nodes, which may greatly improve the pre-operative planning.[26-33] In colon cancer MRI might also be useful, although it has no role in the planning of pre-operative chemo- or radiotherapy, as this is not indicated in colon cancer. Compared to rectal cancer, the local situation in colon cancer is much more permissive to do an extended resection when necessary. In addition, the local recurrence rate is much lower in colon cancer compared to rectal cancer. Until there is evidence of a benefit of pre-operative chemotherapy in stage II colon cancer, there is no indication for USPIO-MRI. One study showed that MRI lymphangiography is a useful technique for the detection of sentinel lymph nodes.[34] However, we do think that intra-operative sentinel node detection with patent blue is a much cheaper, quicker and easier technique, which should not yet be replaced with expensive pre-operative MRI scans in patients with colon cancer.

Besides the need for enough lymph nodes in the surgical and pathological process, ultrastaging and pre-operative imaging, we should probably exploit our knowledge of tumor genetics and biology to select the appropriate patients for adjuvant treatment. Molecular biological factors might help to select stage II + III patients at risk and those who are sensitive to and benefit from 5-FU based adjuvant therapy. This has already been done in breast cancer.[35-37] In colon cancer, several studies showed that it was possible to predict stage II cancer prognosis by tumor gene expression profiling.[38,39] It is not known yet, if the patients identified with this gene expression profiling benefit from adjuvant therapy. Further study is needed on this subject. Apart from identifying high risk patients, gene expression might help in identifying patients who benefit from adjuvant therapy. For example, patients with high thymidylate synthase (TS) expression levels benefit from

chemotherapy, whereas patients with low TS expression levels have a worse outcome when treated with FU-based chemotherapy. [40] Another option is to treat patients with a therapy based on biological characteristics of the tumour. A start in this area has already been made by treating stage IV colon cancer patients with signal transduction inhibitors like bevacizumab (anti-VEGF) and cetuximab (anti-EGFR).[41,42] These drugs still need to be tested in large trials in stage II and III patients.

Not all patients receiving adjuvant treatment benefit from the therapy. In spite of the treatment with adjuvant therapy some patients will develop metastases still, while others will never develop metastases in the course of their disease, with or without this adjuvant treatment. [43] On the other hand, some of the 20-30% of the patients with a stage II tumor who develop recurrent disease might have had a benefit from the adjuvant treatment for which there was no strong indication according to the current guidelines. The great challenge for the future is to develop better selection criteria for adjuvant treatment, thereby reducing the group of stage III patients who do not benefit at all from the treatment and maybe add an extra group of patients in the current stage II high risk group. At the moment, lymph node status is the best criterion we have to predict the course of the disease. But with the current advances in genomics and proteomics, it is likely that within the coming years it is possible to genotype and phenotype tumors to determine prognosis based only on analysis of the primary tumor.[44] This analysis might be much more informative than lymph node status and adjuvant therapy could probably be based on the results of this genetic mapping. However, nowadays in colon cancer, genomics has not been fully developed yet. And until it is, surgeons as well as pathologists should concentrate on accurate lymph node staging in which as much lymph nodes as possible are examined in a diligent way.

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