Staging in colorectal cancer

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Colorectal cancer is one of the leading causes of mortality and accounts for approximately 200,000 deaths per year in Europe and the USA. An estimated 92% of colon cancer and 84% of rectal cancer patients undergo resection of which the vast majority is performed with curative intend. In guidelines for colon and rectal cancer surgery a surgical consensus statement published in the *Journal of the National Cancer Institute* in 2001 (583–596) the origin of the rectum was defined as being 12 cm from the anal verge by rigid proctoscopy, but the distal border at the point of transition to the anal canal was not defined. This definition of the rectal proximal border was considered justifiable on a biological rather than the anatomical basis, because clinical observations indicate that patterns of recurrence of tumours at greater than 12 cm are more consistent of colonic cancers than rectal cancers. In general four major anatomic divisions of the colon are recognized: the right ascending colon, the middle transfers colon, the left descending colon and the sigmoid colon.

The best estimation of prognosis in colorectal cancer is related to the anatomic extent of disease determined on pathologic examination of the resection specimen. The TNM staging of the American Joint Committee on Cancer and the International Union against Cancer is universally recommended. By definition, the TNM-categories describe the anatomic extent of malignant tumours that have not been previously treated and the predictive value of the corresponding TNM stage groupings is based solely on data deriving from outcome studies of such tumours after complete surgical resection. The most important aspect in surgical staging is known as the R-classification: R0, no residual tumour; R1, microscopic residual tumour; R2, macroscopic residual tumour. The potential margins include the proximal margin, the distal margin, the mesenteric margin and when appropriate, by crucial in rectal cancer, the circumferential (radial) margin ' CRM' . The CRM represents the retroperitoneal or peritoneal adventitial soft tissue margin closest to the deepest penetration of tumour or lymph node metastasis. The CRM should be regarded as positive, if the distance between the deepest extent of tumour and the closest CRM measures 0–1 mm on microscopic examination. In the Dutch trial of radiation and total mesorectal excision versus TME alone for rectal cancer, the risk of local recurrence was related to the CRM measurement as follows: CRM >2 mm recurrence risk 6%, CRM $\leqslant$2 mm recurrence risk 16%, CRM $\leqslant$1 mm recurrence risk 38%. Based on these data and further follow-up it is recommended that a cut off point for assigning margin negativity should be 2 mm rather than 1 mm, but at this moment the 1 mm is still the recommended cut point.

The value of macroscopic description of the resected specimen

Pathologic evaluation of the degree of intactness of the mesorectal surface has been shown to correlate clinically with both local recurrence, distant recurrence and survival and pathologically with CRM involvement. Specifically, an incomplete mesorectum on gross pathological examination has been found to predict higher rates of CRM involvement and local recurrence and lower survival rates as compared to complete or nearly complete mesorectum. Thus the macroscopic quality of the rectal resection specimen as judged by the amount of extramural soft tissue with the mesorectum envelope and the degree of the intactness of the mesorectal fascia directly reflects the adequacy of the surgical technique and correlates with clinical important predictors of outcome.

The chances of a R0-resection with a complete mesorectal specimen can be enhanced by not only better surgical training, but also by better preoperative staging. Specifically in rectal cancer, the choices after the diagnosis of rectal cancer has been confirmed, are transanal local excision, primary total mesorectal excision, preoperative neo-adjuvant (chemo)radiation followed by radical surgery and a tailor-made strategy

for patients with known distant metastasis or severe co-morbidity. In the past, local staging was based on digital examination with terms like "fixed" or "tethered" that have no uniform definition and should no longer be used. Imaging modalities today include endorectal ultrasonography, multislice computer tomography and magnetic resonance imaging with a phased-array coil. For the small lesion the best modality with acceptable accuracy for determining invasion into the layers of the bowel wall is endorectal ultrasonography. Visualisation of the endopelvic fascia and its relationship to the primary tumour is especially important in T2 and T3 tumours. Modern CT but especially MRI have the capacity to show this important fascia, so that a selective approach with regard to preoperative radiotherapy can be used. T3 tumours with endopelvic fascia infiltration or a relationship closer than 2 mm and especially T4 tumours should be treated by chemoradiation with a delay of 4–6 weeks aimed to downsizing and downstaging. After this approach tumours should be restaged in order to ensure a R0-resection. Distant metastatic sites should be excluded by ultrasound or CT of pelvis (liver) and plain chest X-ray. The use of PET-scanning is warranted only in recurrent disease.

Staging by sentinel node biopsy in colorectal cancer patients

The sentinel node biopsy (SNB) in colorectal cancer patients is still under development. In contrast to breast cancer, SNB in colorectal cancer is not performed to avoid a necessary lymph adenectomy but to enable focussed examination of a few lymph nodes. An important consequence of intra operative SNB in colorectal patients is the identification of aberrant lymphatic draining patterns in up to 14% of the patients leading to an adjustment of the initial surgical resection plan. Blue dye is used in most of the studies with moderate variations in volume and site of injection, however the number of the detected SN' s vary. We showed that patients with CEA RT-PCR negative lymph nodes had a significantly better five years disease-free survival, than patients with positive lymph nodes (91% vs 50%), which was confirmed by three other studies. At this moment, however, although it leads to a profound upstaging consequent adjuvant treatment decisions are still unclear. Quality control leading to standardization of SNB and minimal residual disease assessment by bone marrow aspirates and blood sampling is necessary to enable reliable comparison of different studies. Only in this way will this new easily applicable staging method gain its potential role in pre- and postoperative staging of colorectal cancer. Over the past few years there have been major advances in our understanding of the molecular basis of colorectal cancer in its progression which hold potential for translation into novel strategies and staging. Technical advances such as real time polymerase chain reaction and micro-array techniques coupled to the molecular pathways in colorectal cancer makes it possible to develop these new clinical tools. Micro-array analyses are expected to play a major role in the implementation of genome-base tailor-made medicine. Through the evaluation of large scale gene expression profiles, tumours can be classified and important molecular pathways can be found. These developments stress the importance of tumour banking in relation to treatment related randomised controlled clinical trials. In the past years genetic alterations (p53, k-ras lesions involving chromosome involving 18q, micro satellite instability) enzymatic activities (thymidylate synthase), dihydropyrimidine dehydrogenase, thymidinephosphorylase, neo-angiogenesis-related markers (vascular endothelial growth factor, micro vessel density) and lymphocyte infiltration have been investigated. However none of these biomarkers have been proven to be fit for use in clinical practice as a prognostic and staging tool. Recently, the discovery, identification and characterization of potential cancer associated biomarkers has improved advances in proteomics, especially through the development of platforms that permit rapid fingerprint profiling of multiple biomarkers. Proteomics is based on separation and visualisation of complex protein mixtures generally by 2D gel electrophoreses and identification of individual proteins by mass spectrometry and database searching. This novel proteomic approach will provide the clinician with simple and effective methods for early tumour detection, treatment monitoring prognostication and follow-up. Together with present staging methods this could lead to further development of tailor-made treatment approaches.

The role of preoperative imaging in staging colorectal cancer patients

Whereas it has been customary to do some form of preoperative staging for distant metastases in colorectal cancer, the role of locoregional imaging has been less clear. Recently however the advantages of assessing risk factors for local recurrence by preoperative imaging are increasingly recognised, especially for rectal cancer.

Locoregional staging

The two foremost important factors that influence local recurrence rates after resection of a rectal cancer, apart from the height of the tumour, are the local tumour extent and the nodal status [1]. The local tumour extent is traditionally classified with the pathological T staging system, in which T3 and T4 tumours are considered to have a higher risk for local recurrence. Maybe even more important is the actual distance of the tumour to the mesorectal fascia, as the CRM has repeatedly been shown to be closely related to local recurrence [2–4]. For the locally advanced cases with in-growth in other organs planar imaging provides an accurate anatomical road map for the surgeon. Endo rectal ultrasound ' EUS' is very accurate for assessing the depth of tumour ingrowth in the bowel wall but is less accurate for staging the more common tumours that penetrate the bowel wall [5–10]. Because of the limited field of view it is difficult to visualize the mesorectal fascia, a structure that has become increasingly important to assess the anticipated circumferential resection margin. As it is a real time investigation, the images are of little use for the surgeon or radiotherapist when treating a more advanced cancer. Another drawback of EUS is that its performance depends on the skill of the observer with quite a long learning curve [8,11,12]. Planar imaging techniques such as CT and MRI do not share these disadvantages. Especially MRI with a phased-array coil has emerged as a highly accurate tool to provide anatomical information of the entire pelvic region. The advantage of an intrinsic high soft tissue contrast resolution combined with new technical developments (faster acquisitions, dedicated external coils, contrast agents etc.) has made MRI the most promising technique for local staging of rectal cancer [13–20].

Until very recently MRI has been the only modality that had been tested for the prediction of the CRM in single center studies [16–19]. The results of a systematic review of all published data so far clearly shows that MRI performs very well in predicting the CRM in rectal cancer surgery [21]. From the individual studies however it is still unclear how often the information of MRI influenced the treatment, and how this was dealt with in the analysis. An audit of data on outcome of rectal resections in one of the authors' department has shown that with standard use of MR in the preoperative work-up the proportion of incomplete resections has been reduced by half, through better selection for neoadjuvant treatment and extensive surgery [22]. Whether or not the excellent MR results

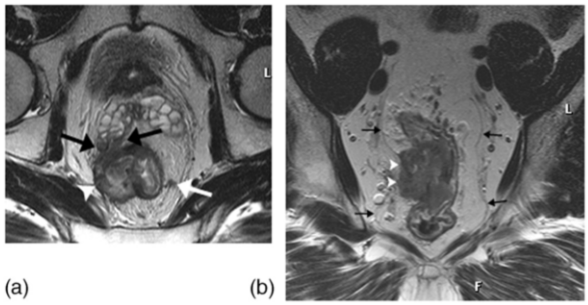

Fig. 1. "What you see is what you get": (a) Axial T2W FSE MR image of a male patient with rectal cancer shows tumour involvement of the mesorectal fascia (white arrowhead), obvious invasion of the right seminal vesicles (black arrows) and a suspected mesorectal lymph node (white arrow). (b) Coronal T2W FSE MR image of the same patient clearly visualizes the mesorectal fascia (black arrows) and tumour penetration through the mesorectal fascia (white arrowheads). All MR predictions were confirmed at histology.

of single center series are applicable in routine clinical practice has been the subject of a multicenter European study (Mercury trial). Although at present we are awaiting the definitive results, preliminary results of 715 patients studied in 11 European centers show that MRI agreed in 82% with histology for the prediction of an involved (CRM <1 mm) mesorectal fascia and that the difference between MRI and histology for the assessment of depth of tumour invasion beyond the bowel wall was –0.046 mm (95%CI: 0.487–0.395). These results suggest that after a short learning curve MRI is reliable in a general setting and that the basic message for MRI imaging of primary tumour extent is that ' what you see is what you get' [23,24] (Fig. 1, Van Laar).

CT is more available and faster than MRI, and it allows local and distant staging in one single examination. With the new multislice spiral CT technique the resolution of the images is improved and modern CT may become clinically competitive with MRI. The question however is, whether CT will ever be a serious competitor of MRI given the inherent better contrast resolution of MRI. The SPICTRE (Spiral CT in Rectal Cancer) study is a Dutch multicenter study that has investigated the distance of the tumour to the mesorectal fascia with a modern CT technique. The preliminary results suggest that CT can be used for prediction of the CRM in tumours located in the middle and high rectum, but that CT is less accurate than MRI for low rectal cancer, where the rectum is surrounded only by a very thin fat stripe [25].

For the detection of nodal disease CT has never been a powerful tool. Only relying on size and shape criteria, CT cannot accurately distinguish between malignant and benign lymph nodes. The specific

problem in rectal cancer lymph node metastases is that there are many small (<5 mm) nodes that may contain metastases [26]. EUS uses both size and echogenic features to determine the malignant potential of lymph nodes and performs slightly better than CT. EUS-guided fine needle aspiration has been reported to be a very reliable method with accuracies up to 100%, but it is a cumbersome technique that will not gain widespread acceptance [27]. Recent developments have shown that MRI with its inherent superior soft tissue contrast resolution may be the most promising modality for distinguishing between the lower risk N0 and higher risk N1 and N2 rectal cancer patients. New MR contrast agents, like Ultra small Super Paramagnetic Iron Oxide (USPIO) may in the near future help radiologists solve this difficult problem [28,29].

Harisinghani et al. [29] studied USPIO MRI in patients with resectable prostate cancer and the node-by-node analysis in 334 lymph nodes showed a sensitivity of 91% for USPIO MRI as compared with 36% for non-enhanced MRI. At present there are only one published and a few unpublished pilot single center studies on the use of USPIO in the detection of nodal metastases in rectal cancer, nonetheless all showing promising results [28]. Further research is necessary to determine whether MRI will be the most effective non-invasive predictor of one of the major risk factors of rectal cancer patients: nodal involvement. Recently, a multi center study has been initiated in the Netherlands, funded by the Dutch Cancer Society, testing USPIO-enhanced MRI for its accuracy and consistency in predicting the nodal status of rectal cancer both in specialist centers and general hospitals.

New techniques in diagnostic oncology like PET-CT imaging combine functional with anatomical imaging. So far the scarce publications on hybrid PET-CT show disappointing results for N-staging in rectal cancer. Heriot et al. [30] demonstrated a sensitivity of only 29% for predicting lymph node involvement, probably related to the limitation of PET-CT in detecting low-bulk disease.

Distant staging

Despite some improvements in the technique, ultrasonography remains poor in sensitivity for the detection of colorectal liver metastases (40–69%) [31]. Therefore its role should be limited to screening those patients that have a low prevalence for liver metastases.

As modern multislice CT scanners can generate images of the chest and abdomen in one breathhold, it has become a very effective tool for screening distant metastases and with a sensitivity varying between 70–85% CT is the second most sensitive non-invasive diagnostic tool for detection of liver metastases, after contrast enhanced MRI [32].

When the functional information of FDG-PET is added to the CT images in hybrid whole body PET-CT imaging the sensitivity for lesion detection is further improved [30,33]. Apart from some promising single center results, multicenter studies and especially cost-efficiency analyses on expensive diagnostic tools such as PET-CT for distant staging of colorectal cancer are still lacking. Other imaging techniques are meanwhile evolving at a fast pace so before PET-CT has got the chance to prove itself it is already competing with another whole body technique: whole body MRI with moving bed equipments.

Whole body MRI (WB MRI) will become a serious competitor to PET-CT for distant staging of colorectal cancer patients for several reasons. MRI is less costly than hybrid PET-CT and there is no exposure to radiation. The main advantage of MRI however lies in the use of iron oxide-based contrast agents. Iron oxide contrast enhanced MRI is not only very promising for the detection of lymph node metastases, it has also shown to be one of the most accurate noninvasive preoperative imaging tools for the detection of colorectal liver metastases [34]. A whole body USPIO-enhanced MR in a patient with rectal cancer would therefore not only accurately show the local extent of the tumour and nodal invasion, but also the distant spread of tumour into the liver and lungs in one single examination, obviating the need for other imaging studies, like chest X-ray, US, CT or PET-CT (Fig. 2, vd Varst). Preliminary results of a comparative study in rectal cancer patients performed at the university hospital Maastricht shows that WB MRI was equal to PET-CT for the detection of liver and lung metastases. Further studies on a larger scale are required to establish the most cost-effective whole body technique for a one-shop-one-stop locoregional and distant staging of colorectal cancer.

Conclusion

In conclusion, there is an increasing role for imaging in the preoperative locoregional staging of rectal cancer. MRI is the most promising imaging modality to assess the important risk factors for local recurrence: distance of the tumour to the mesorectal fascia,

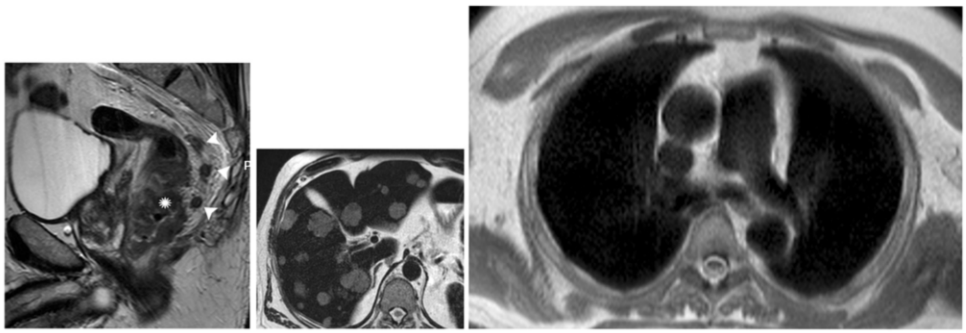

Fig. 2. "Whole Body USPIO enhanced MRI is a promising tool for one-shop-stop staging of rectal cancer patients ": (left) Sagittal T2W FSE MR image of a male patient shows a distal rectal tumour (white asterisk) with suspected mesorectal lymphnodes (white arrowheads). (mid, right) Axial T2W MR images of the same patient of the liver and lungs show multifocal liver lesions suspected for metastases and no lung metastases.

T stage and nodal disease. When a high accuracy is confirmed in large multi-center studies, MR can be used to apply differentiated neo-adjuvant treatment, i.e. no radiotherapy for the low risk, 5×5 Gy for the intermediate risk and a long course of chemo-radiation for the high risk patients. For distant staging the present gold standard of CT will be challenged by whole body techniques such as PET-CT, and more likely iron oxide contrast enhanced MRI.

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