The multidisciplinary treatment of rectal cancer: pathology

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introduction

In the multidisciplinary treatment of rectal cancer various disciplines are involved to make treatment decisions. Pathology is one of them, being involved in both preoperative and postoperative patient evaluation. In the current review the preoperative role is described briefly and it focuses mainly on the postoperative evaluation. This evaluation is not only the assessment of tumour invasion, margins and lymph node status but effects of neo-adjuvant therapy and surgical technique can be judged as well and have profound clinical value. Moreover, based on certain histological characteristics further treatment decisions can be made.

initial treatment decisions

In the era of potential extensive neo-adjuvant therapy, the histological diagnosis of rectal adenocarcinoma on pre-treatment biopsy has become even more important. Most textbooks describe the criteria for this diagnosis accurately. Classification of carcinomas has only limited importance. In cases of mucinous carcinoma, imaging, performed to judge tumour extension, is less reliable. As a consequence, the subsequent risk on involved resection margins is higher (Figure 1).

Features that point to the presence of Lynch syndrome (formerly referred to as hereditary non-polyposis colorectal cancer) can be detected morphologically and by using immunohistochemistry for expression of mismatch repair genes. However, these features are generally determined in the resection specimen and the subsequent mutation analysis requires too much time to be of use in the initial treatment planning.

Up to now, no prediction can be made based on the biopsy about the response to therapy, although a number of attempts have been made to do so. Detailed examination of the biopsy is required to determine the possibility of a Transanal Endoscopic Microsurgical procedure (TEM) instead of a Total Mesorectal Excision (TME).

In tumours limited to the submucosa with a low likelihood of metastases staged as uT1 by ultrasound, there is a possibility for local excision of the tumour. This technique was initially developed for the removal of adenomas, but is of use in patients with only superficially invasive carcinomas as well. However, when a local excision is performed chances of local recurrence are higher than after a radical excision [1, 2].

A number of national guidelines limit TEM to those patients with uT1 and a good to moderate differentiation grade in the biopsy, making the determination of differentiation grade in the pre-treatment biopsy important. The excision specimen requires careful examination in order to determine the need for re-excision, which should be performed in case of margin involvement, unexpected higher T stage and histological high-risk tumours. In a recently published study by Borschitz et al [3] it is shown that local recurrence rates vary according to histological features as determined in the resection specimen. The local recurrence rate in patients with high-risk histology (poor differentiation, lymphatic or angioinvasion) is 20% compared with 6% in the low-risk group. Highest local recurrence rates (46%) are present in patients with involved resection margins.

In addition, since no lymph nodes can be investigated, the presence of systemic disease needs to be predicted on features of the primary tumour. In general, the risk of lymph node metastases for pT1 tumours is low, varying from 6 to 13% [4–7]. Classical risk factors are poor differentiation [4, 6–10], lymphatic and angio-invasion [4, 5, 8–10] and invasion depth [4–6, 8–10] (Figure 2).

Recently, a number of papers [4, 7, 8, 11, 12] have emphasized the importance of the histology of the invasive front of the tumour, with dedifferentiation and budding as inverse prognostic factors, associated in 15–56% with the presence of lymph node metastases.

A new trend in local treatment is the addition of neo-adjuvant therapy to local excision. Indeed, local recurrence rates are much lower, but the histological criteria on which further treatment decisions are made are yet unclear.

evaluation of treatment

While in the 20th century the evaluation of treatment was limited to the assessment of resection margins of the operation specimen, in the current century innovations in the multimodality treatment of rectal cancer patients are reflected in the increasingly complex evaluation of specimen, both on macroscopic and microscopic evaluation. Studies in recently completed large multi-centre trials have confirmed the importance of evaluation of the quality of the resection specimen [13–15] and the assessment of the circumferential margin (see below). These trials increasingly include...
neo-adjuvant therapy, challenging the pathologist to improve the information obtained from the resection specimen. The main challenge lies in the evaluation of treatment response and prediction of clinical outcome based on these data.

Various types on neo-adjuvant therapy have been developed, varying from short-term preoperative radiotherapy [5x5 gray (Gy)] with a short interval till the operation, to long-term schedules in which 50.4 Gy of radiotherapy is combined with chemotherapy. The latter is aimed at tumour down-staging. No down-staging is found in patients who had surgery within a week to 10 days after the start of the short-term regimen [16].

To establish a complete response or tumour regression can be reproducibly measured using the above mentioned criteria, partial regression and absence of regression are much more difficult to assess reliably. Various systems for tumour regression have been described, using relative percentages, the amount of fibrosis and the ease with which tumour cells can be found. Usually, the system consists of five categories, but no correlation with prognosis was demonstrated using these five categories. Gathering them together in a three-tiered classification results in some studies in a relation with prognosis [19, 21, 22], but the results are not consistent. If regression is scored by more than one pathologist, reproducibility is poor and, in addition, intra-individual variation is also present. Unless these issues are solved and a standardized method of regression grading has been developed, the value of regression grading for daily clinical practice is limited.

The aim of long-term neo-adjuvant therapy is to facilitate surgical resection of the tumour and the surrounding mesorectal fat. Therefore, it makes sense to evaluate surgery-related factors to determine the success of the adjuvant therapy. The most important factor is the circumferential or lateral resection margin (CRM). A large number of studies have analyzed the importance of this margin for local recurrence as well as for survival. Its importance after neo-adjuvant therapy was not clear, since it was thought that this kind of therapy could compensate for positive margins by ways of sterilizing the tumour remnants left behind. However, evidence is accumulating for the opposite: in a recent review (Nagtegaal and Quirke, unpublished data), in which data of 17 568 patients on CRM involvement are summarized, it has been demonstrated that the prognostic power of CRM involvement is increased after neo-adjuvant therapy (Figure 3). In addition, several studies value the CRM over tumour regression grading. As been suggested that CRM involvement might function as an alternative endpoint in neo-adjuvant clinical trials.

The most important factor in rectal cancer surgery is CRM involvement. As has been discussed above, involvement is predictive of poor outcome, with an increased risk of local recurrence, distant metastases and decreased survival. The CRM positivity might be due to advanced tumour growth, with a poor response to therapy or poor preoperative imaging. Another possibility is inadequate surgery (Figure 4). The quality of rectal cancer surgery can be defined by the plane of dissection. A well-performed TME has a mesorectal plane of resection. When the plane of resection is on the muscularis propria instead, the chances of CRM involvement are much higher. The quality of surgery examined after neo-adjuvant therapy are usually low, but their examination is important.

Figure 1. Relation of tumour type with circumferential resection margin involvement. In mucinous carcinomas with a mucinous component of 95–100%, positive margins occur in 45% of patients compared with 16% in non-mucinous carcinomas. Data from the Dutch TME trial.
has been evaluated in four different studies \[13, 15, 24, 25\] (Figure 5), including a study using laparoscopic surgery. No differences were observed between the laparoscopic surgery and open surgery. Three of those studies correlated plane of resection with outcome (Table 1) and found a strong correlation with local and overall recurrence. There have also been reported differences in survival, but these are not significant due to the relatively short follow-up period.

**Figure 2.** Prognostic factors for the presence of lymph node metastases in T1 rectal cancer. Data are presented as hazard ratio and 95% confidence interval.

**Figure 3.** Prognostic impact of circumferential margin involvement. Data are presented as hazard ratio and 95% confidence interval.

**Further treatment decisions**

While the above mentioned parameters for assessment of surgical procedures are firmly established, there is less evidence for factors on which further treatment decisions are based. One example is the indication for adjuvant therapy in stage II tumours. Routine use of adjuvant therapy...
is not recommended, because of the relatively low risk on development of metastases. However, certain subgroups might benefit from therapy. By consensus, ASCO [26] and other international and national guidelines suggest that high-risk stage II tumours (characterized by T4 stage, perforation or obstruction, poor histological grade, few examined lymph nodes and/or peritumoral lymphovascular invasion) may be considered for adjuvant therapy. Although these factors are established prognostic markers, their predictive value is yet unknown.

Potentially, tumour response on neo-adjuvant therapy might predict the success of subsequent adjuvant therapy. Preliminary results from the EORTC 22921 demonstrate a benefit of chemotherapy in the subgroup of patients that show down-staging. Whether tumour regression grading might play a predictive role needs to be investigated.

Many studies have been performed on potential predictive factors. At present none of these is robust enough to be used in routine clinical practice. We expect however, that in this era of targeted therapy such markers will become available in the near future.

**Conclusion**

The role of pathology in the multidisciplinary treatment of rectal cancer has expanded during the last 20 years. Factors that evaluate treatment, like CRM involvement, have been firmly established. Initial treatment decisions and future decisions about adjuvant therapy are at present only partly based on pathological examination of diagnostic biopsies. However, research is ongoing focusing on predictive factors for adjuvant and neo-adjuvant therapy. Before long, such markers will be available, thus making the role of pathology even more important.

**Acknowledgements**

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Table 1. Prognosis in relation to quality of surgery (plane of resection)

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<td></td>
<td>Local recurrence</td>
<td>Overall recurrence</td>
<td>Survival</td>
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<tr>
<td>mesorectal fascia</td>
<td>9%</td>
<td>22%</td>
<td>86%</td>
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<td>mesorectal fat</td>
<td>(previously: good/complete)</td>
<td>(previously: intermediate)</td>
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<tr>
<td>muscularis propria</td>
<td>15%</td>
<td>36%</td>
<td>76%</td>
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<tr>
<td>(poor/incomplete)</td>
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<td>P-value</td>
<td>n.s.</td>
<td>P = 0.01</td>
<td>n.s.</td>
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references

12. Goldstein NS, Hart J. Histologic features associated with lymph node metastasis in stage T1 and superficial T2 rectal adenocarcinomas in abdominoperineal resection specimens—Identifying a subset of patients for whom treatment with adjuvant therapy or completion abdominoperineal resection should be considered after local excision. Am J Clin Pathol 1999; 111: 51–58.