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 ypT0, initially five blocks
of the tumour area are required. If no tumour is found in
these first five tissue blocks, the entire tumour area should be
included for histological examination (blocked), and if still no
tumour is found, three levels should be cut to exclude the
presence of tumour (P. Quirke, personal communication).
This procedure has unfortunately up until now rarely been
used.

In the absence of the primary tumour, positive lymph nodes
can still be found (ypT0N1); percentages in the literature vary
from 0 to 19% [17–20]. The numbers of lymph nodes
examined after neo-adjuvant therapy are usually low, but their
examination is important.

While 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. It has 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
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.

**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

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**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.
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

Iris Nagtegaal is a fellow of the Dutch Cancer Society.
Table 1. Prognosis in relation to quality of surgery (plane of resection)

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<tr>
<td></td>
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<td>Overall recurrence</td>
<td>Survival</td>
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<tr>
<td>Mesorectal fascia (good/completeness)</td>
<td>9%</td>
<td>22%</td>
<td>86%</td>
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<td>Mesorectal fat (intermediate)</td>
<td>15%</td>
<td>36%</td>
<td>76%</td>
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<tr>
<td>Muscularis propria (poor/incompleteness)</td>
<td>15%</td>
<td>36%</td>
<td>n.s.</td>
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P-values:
- Nagtegaal 2002: P = 0.01
- Quirke 2005: P = 0.0019
- Maslekar 2007: P < 0.001

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.