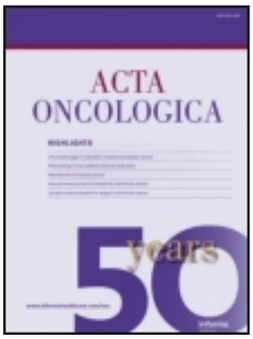

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EDITORIAL

The 'good', the 'bad', and the 'ugly' rectal cancers

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Some decades ago, patients with a newly diagnosed rectal cancer were locally staged clinically, using the finger and a rectoscope. If the tumour was judged resectable, patients were operated upon whereas those judged not possible to resect were referred for preoperative radiotherapy. Delayed surgery was then performed if the tumour had diminished in size or was no longer clinically fixated by rectal palpation. In those days, 30–40% of the rectal cancers recurred locally even if surgery was successful. This often resulted in severe suffering prior to death. Five-year survival was less than 40% [1–3]. Since then, most aspects of the care of rectal cancer patients have improved. The introduction of more precise surgery, total mesorectal excision (TME), and the use of pre- or postoperative radiotherapy or radiochemotherapy have contributed both to much lower local recurrence rates and improved survival. Presently, population-based studies can report local recurrence rates less than 10% and 5-years survival of 60% [4–7]. Radiotherapy, alone or with chemotherapy is given not only to the 10–15% non-resectable cancers but also to many less advanced tumours since it lowers local recurrence rates and improves survival [8,9]. Such comparably low levels of local recurrence rates can not be achieved if preoperative radiotherapy is only given to the most advanced T4 tumours [10].

The availability of different treatment options, each having pros and cons (particularly concerning late adverse effects [11]), has resulted in an increasing demand on better preoperative staging. Through the years, the possibilities to stage rectal cancer have also improved, although not introduced into clinical routine as rapidly as other aspects of care. Clinical staging, by evaluating fixation to the surrounding tissues is still used to identify locally advanced pelvic disease and to select patients for different preoperative treatments. The limitation of the clinical examination is obvious. In the case of large pelvic masses the mass effect of the tumour may cause fixation without corresponding tumour infiltration. There is also an obvious limitation of the clinical examination regarding estimation of tumour extent to different anatomical structures, some of them not reachable by the examining finger.

The different imaging techniques, used during the past decades to locally stage rectal cancer [12], have to a various extent adopted pathological staging systems and used histopathology as a standard of reference to estimate sensitivity and specificity. In transrectal ultrasonography this had resulted in a uT-staging system, corresponding to the pathological pT-staging system. The sensitivity, specificity and limitations of different imaging techniques to stage early rectal cancer with pathology as a standard of reference is extensively documented, however, mostly in single-centre studies [12]. In contrast, these parameters are not as well known for the locally advanced rectal cancers, since many of the surgical and pathological examinations of these tumours are performed after preoperative treatment with an effect on tumour stage [13–15].

More recently, the circumferential resection margin (crm), the mesorectal fascia and the remaining

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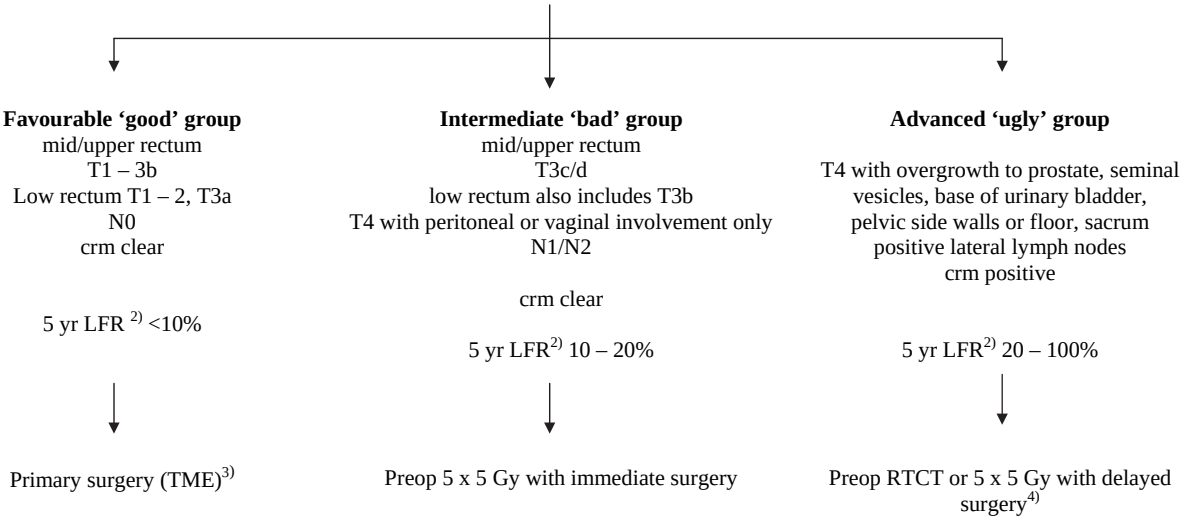
lateral and inferior borders of the mesorectum have come into focus when staging rectal cancer. The ability to identify these landmarks by dedicated pelvic MR-imaging as well as predicting the degree of extramural tumour extension was the basis for the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study [16,17]. The positive experiences using a dedicated protocol for MR-imaging of rectal cancer in the study have resulted in ongoing discussions to stratify patients with rectal cancer based on MRI to be used for selection to preoperative treatment. In this issue of Acta Oncologica, Smith and Brown discuss preoperative staging of rectal cancer and present an algorithm for dividing the rectal cancers into three groups [18]. The rectal tumours are then divided into those having no bad prognostic factors on MRI, neither for the risk of local or systemic failure ('good group', those having features on MRI suggesting increased risk for distant metastases ('bad') or those with features suggesting high risks for local recurrence and distant metastases ('ugly'). The characteristics are depicted in figure 9 in [18]. The new imaging aspects in this stratification are the extent of extramural extent of tumour in mm, the relation to the mesorectal fascia, the presence of more than four lymph node metastases and extramural vascular invasion. It is then important to recognise that beside extramural tumour extension and relation to the circumferential resection margin, the remaining prognostic factors evaluated by MRI are yet only reported by single centres.

The algorithm was used in a phase II trial, EXPERT, at the Royal Marsden Hospital, London, UK [13], and is presently used in a multicentre randomised phase II study, the EXPERT-C protocol. In the trials, the 'bad' and 'ugly' groups are first given neo-adjuvant combination chemotherapy (capecitabine and oxaliplatin), then radiochemotherapy with capecitabine, surgery and postoperative chemotherapy, without or with cetuximab in the ongoing trial. The 'good group', not included in the trial, is operated upon, and postoperative therapy is given only if the pathological examination shows unfavourable signs. The neo-adjuvant chemotherapy is experimental but aimed at reducing the risk of systemic failure more efficiently than only postoperative chemotherapy can do. It is thus logical that the two groups included in the trial are characterised by high risks of systemic failure.

We have during the past years in Stockholm and Uppsala used a slightly different definition, adjusted to the therapy tradition in Sweden, presently emphasizing the local failure risk [19]. Thus, a favourable, 'good' group has a low risk of failing locally, an intermediate 'bad' group has higher risk of failing locally and an advanced 'ugly' group has the highest risk of failing locally. The characteristics and the choice of therapy are shown in Figure 1 . The difference between our definition and the one suggested by Smith and Brown [18] is in the definitions of the 'bad' and 'ugly' groups. We have not considered vascular invasion as a sign indicating increased risk of local failure and have therefore not incorporated that feature into the algorithm. It may be an important sign of systemic disease[20], however, this has practically not yet had any influence on the choice of preoperative therapy. Besides the previously most locally advanced tumours corresponding to the 'non-resectable T4s', growing into adjacent organs, we also include the tumours growing adjacent to the mesorectal fascia (crm+) to the advanced, 'ugly' group. The group at Royal Marsden Hospital, as most other international groups also tend to do, refer both the 'bad' and the 'ugly' tumours to the locally advanced cancers. Actually, the 'non-resectable' tumours, or the T4s growing into adjacent structures, have been excluded from all recent trials in these patients [13,21–25]. They are also excluded from the ongoing EXPERT-C study, even if they have the greatest needs for more intensive, experimental therapy. Few studies have recently focused on the most advanced tumours [14,26–28].

The use of imaging to identify patients regarded as having locally advanced rectal cancer has resulted in a shift towards including more and more patients as having this condition. The possible increase in number of patients regarded as having locally advanced rectal cancer due to ′staging drift′ must be taken into consideration when evaluating the effects of treatment of the disease. This is particularly relevant when conclusions are made from phase II studies exploring new treatments (many phase II studies published the past few years, none cited). It is possible that patient selection is more important than treatment efficacy [29]. This 'staging drift' may be obscured if imaging as well as imaging interpretation is not strictly standardised using pre-study workshops and monitoring as described in the MERCURY-study.

In the future, there is a need to purify and more strictly standardise the term LARC. Using imaging, and in particular dedicated pelvic MR-imaging, this is possible provided that quality assurance, by workshops and by involvement of radiologists in the multidisciplinary teams is established. Due to the different approaches of treatment offered by radiotherapy alone as to RTCT, it is reasonable to divide the locally advanced rectal cancers into level 1 or 2 depending on whether radiotherapy or radiochemotherapy should be used prior to surgery.



[1] The algorithm does not primarily address the risk of systemic disease, although this risk also increases with the presence of many of 'the risk factors', however, not necessarily parallel to the local failure rate (LFR).
[2] Calculated in the group of patients planned for surgery, i.e. irrespective of the surgical outcome. The figures are valid if the surgeon is an experienced rectal cancer surgeon and no pre-treatment is given.
[3] A local procedure is possible in a few (chiefly pT1, sm1 + 2, N0).
[4] RTCT means radiochemotherapy to 50.4 Gy in 1.8 Gy fractions with 5-fluorouracil. 5 x 5 Gy with delayed surgery is used in patients not fit for RTCT. The relative antitumour efficacy of conventionally fractionated RT or the short-course schedule is not known with any greater certainty [30,31]

Figure 1. MRI-directed pre-operative evaluation practised presently in Uppsala and Stockholm, Sweden.

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