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Consensus statement

Experts reviews of the multidisciplinary consensus conference colon and rectal cancer 2012: Science, opinions and experiences from the experts of surgery

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Abstract

The first multidisciplinary consensus conference on colon *and* rectal cancer was held in December 2012, achieving a majority of consensus for diagnostic and treatment decisions using the Delphi Method. This article will give a critical appraisal of the topics discussed during the meeting and in the consensus document by well-known leaders in surgery that were involved in this multidisciplinary consensus process.

Scientific evidence, experience and opinions are collected to support multidisciplinary teams (MDT) with arguments for medical decision-making in diagnosis, staging and treatment strategies for patients with colon or rectal cancer.

Surgery is the cornerstone curative treatment for colon and rectal cancer. Standardizing treatment is an effective instrument to improve outcome of multidisciplinary cancer care for patients with colon and rectal cancer. In this article, a review of the following focuses; Peri-operative care, age and colorectal surgery, obstructive colorectal cancer, stenting, surgical anatomical considerations, total mesorectal excision (TME) surgery and training, surgical considerations for locally advanced rectal cancer (LARC) and local recurrent rectal cancer

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(LRRC), surgery in stage IV colorectal cancer, definitions of quality of surgery, transanal endoscopic microsurgery (TEM), laparoscopic colon and rectal surgery, preoperative radiotherapy and chemoradiotherapy, and how about functional outcome after surgery?

Keywords: Colon; rectal cancer; Minimal invasive; Laparoscopy; TEM; TME; MRF

Introduction

Surgery is the key curative treatment for colon and rectal cancer. Additionally, palliative surgery offers valuable options to increase a patient's quality of life. Currently, surgical outcome and quality of cancer care are at the top of the list of 'improvement of care' projects. From large observational research, we know that wide variations in patterns of care and outcome exist in the field of surgical oncology.[1–3] The lack of standardization in colorectal cancer treatment was one of the most important driving forces behind the EURECCA initiative some years ago.[4] EURECCA, short for European REgistry of Cancer CAre, aims to standardize and register cancer care to reduce variance between European countries.[4] After three meetings a framework takes shape, which can be used for the implementation of guidelines and subsequent standard approach for patients with colorectal cancer. Theoretically, patients should no longer be at risk of misdiagnosing, under- or over staging, or receiving inappropriate treatment. EURECCA organized its first multidisciplinary consensus meeting held in December 2012 on colon *and* rectal cancer management. This article is one of a series of communications on the consensus meeting. The first article is the Mission statement.[4] The second article is the 'General consensus document'; it describes the epidemiology backgrounds of colorectal cancer, and lists all the actual consensus statements, describes the methodology of the performed Delphi process, and reports the results of the voting (van de Velde et al. Eur J Cancer, 2013 Oct 31, pii: S0959-8049(13)00780-6. http://dx.doi.org/10.1016/j.ejca.2013.06.048). This article presents the views of the surgeons involved in this consensus process. Other expert reviews have been written and will also be published in pubmed and linked as addenda to the general consensus document (van de Velde et al. Eur J Cancer, 2013 Oct 31, pii: S0959-8049(13)00780-6. http://dx.doi.org/10.1016/j.ejca.2013.06.048). The purpose of this article is to support the multidisciplinary teams (MDT) in their choices on colon and rectal cancer management from a surgical perspective.

Colorectal cancer surgery – general considerations

Perioperative circumstances

Fast track protocols in surgery were designed to minimize surgical complications by providing a multimodal approach implementing "as good as possible" evidence based tools to achieve early recovery after major surgery.[5] This was first done for patients undergoing colectomy and later was also implemented to the care for patients undergoing TME or liver surgery. ERAS which is short for enhanced recovery after surgery, focusses on the following standardized protocol elements, improving patient education, reducing pain, reducing nausea and vomiting, stimulating normal diet and get the patient out of bed as soon as possible.[6] Implementation projects resulted in large reduction in length of hospital stay.[6] http://www.erassociety.org/.

The main challenge to optimize perioperative care remains a continuous team effort from patient, surgeon, anaesthesiologists, general practitioner and nurses.

Laparoscopic surgery for colorectal cancer

Introduction

Laparoscopic colorectal surgery has become part of routine daily practice, although implementation varies hugely between and within different European countries.[7,8] Despite increasing level of expertise, not every patient with colorectal cancer will be a good candidate for minimally invasive surgery, mostly because of previous abdominal surgery or locally advanced tumours.

Initial implementation of laparoscopic techniques was associated to several concerns such as oncological safety with respect to radicality, adequacy of lymph node dissection and occurrence of port site recurrences. With emphasis we state that laparoscopic resection of colorectal cancer is technically challenging and requires a defined level of expertise. Nowadays, laparoscopic surgery for colorectal cancer is rendered safe in experienced hands.

Laparoscopic surgery and short-term results

The first randomized studies demonstrated classical short-term advantages of the laparoscopic approach, such as less postoperative pain, less blood loss, faster recovery of bowel function and shorter hospital stay.[9–11] These results were confirmed in a systematic review in 2006 by Reza et al.[12] Complication rate and postoperative mortality did not significantly differ among the two techniques.

A Cochrane review on laparoscopic rectal cancer surgery included 48 studies with a total number of 4224 patients.[13] Laparoscopic total mesorectal excision (TME) resulted in less blood loss ($p < 0.05$; 2 studies), quicker return to normal diet, less pain, less narcotic use and less immune response. No differences in postoperative morbidity, anastomotic leakage or mortality were found. A recently

published trial on rectal cancer confirmed the short-term advantages of laparoscopic TME.[14]

It is important to realize that in these studies routine perioperative care was applied. The laparoscopic approach in a fast track setting showed the shortest length of hospital stay.[15]

Laparoscopic surgery long-term results

No significant differences in overall survival, local recurrence and distant metastasis rates between laparoscopic and open surgery were found in a Cochrane review based on 12 studies, both for colon and rectal cancer.[16] Two trials reported survival rates per tumour stage and no significant differences in survival between laparoscopic and open surgery among stage I, II and III were found.[17,18] However, heterogeneity of follow-up and missing actuarial survival data in 5 studies may have influenced the results of the meta-analyses.

Potential long-term advantages of laparoscopic surgery for colorectal cancer are reduction of incisional hernias and adhesion related small bowel obstruction. A recent population based study from the UK demonstrated a significant reduction in admission or reintervention for adhesions,[19] although data from Swedish patients participating in the COLOR I trial showed no difference in readmission due to adhesions or small bowel obstruction.[17]

Conversion in laparoscopic surgery

The consensus document stated that patients early converted from laparoscopic surgery to open surgery did similar as patients who underwent primary open colon resection, this was agreed with moderate consensus (>70%). Subgroup analyses of the randomized trials suggested negative outcome of conversion from laparoscopic to open surgery, consisting of more blood loss, longer operating time, longer hospital stay, and higher risk of recurrence without impact on survival.[20–22] Methodological shortcomings of these analyses were the comparison of converted laparoscopy with completed laparoscopic procedures instead of open surgery. A learning curve effect in these studies might have been of influence.

It is important to distinguish preemptive (early) conversion from reactive (late) conversion.[23] Preemptive conversion can be considered as a diagnostic laparoscopy followed by open resection. Reactive conversion is a result of a complication during the laparoscopic procedure, such as an uncontrollable bleeding or bowel injury. Preemptive conversion has a similar outcome as open surgery, while reactive conversion has a negative impact on outcome. Conversion rates in the Dutch Surgical Colorectal Audit were 15% and 13% for colon and rectal cancer respectively.[7] Comparing 446 converted laparoscopic resections with 4287 open procedures revealed an almost identical outcome.

Learning curve and quality control in laparoscopic surgery

One of the most important issues in laparoscopic surgery for colorectal cancer is quality control. Miskovic et al. calculated the length of the learning curve for several outcome variables using cumulative sum charts.[24] This length ranged from 87 for the outcome variable blood loss to 152 for conversion. These data underline the need for thorough training in order to be able to independently perform laparoscopic colorectal surgery. This may be organized on a national level.[25] After implementation, quality of laparoscopic surgery can be monitored using clinical auditing.[7]

Costs of laparoscopic resection

Traditionally, laparoscopic techniques have been associated with increased costs. Laparoscopic procedures take more time compared to open surgery, and disposable instruments are used. Laparoscopic resection is saving money by compensating with the short-term advantages.[26,27] A prospective study from England demonstrated that the operative costs were higher for laparoscopic surgery compared to the open approach (£2049 vs. £1263), due to the costs of disposable instruments.[28] However, reduction of hospital stay resulted in reduced hospital costs (£1807 vs. £3468).

Reduce mortality by laparoscopic CRC surgery

Quality of laparoscopic surgery for colorectal cancer in the Netherlands was studied.[7] Patients undergoing laparoscopic resection have a more favourable risk profile in comparison to open surgery patients. After case mix correction, advantages of laparoscopic surgery were confirmed on a population level, and there was even a significantly lower mortality rate compared to open surgery. Other studies suggested that the high risk population will probably benefit most from a minimally invasive surgical procedure. This may explain the discrepancy on mortality between population based data and randomized trials, in which high risk patients are often excluded.[26]

General considerations – advanced age and colorectal surgery

Almost three-quarters of cases with colorectal cancer are people aged 65 or over. As a result of an increasing number of elderly, more octogenarians are presented to the surgeon for operation. Overall survival in elderly with rectal cancer did not improve after introduction of preoperative radiotherapy and TME surgery.[29] From cancer registry data (EUROCARE-4), we know that survival over time was more pronounced in younger colorectal patients than in elderly.[1] Because the group of older patients is very heterogeneous with regard to co-morbidities and fitness, it is difficult to identify patients that have a high risk of adverse outcome after colorectal cancer surgery. Rutten et al. showed that non-cancer related mortality after surgery is a significant problem in the first six months.[29] In the past, many studies have shown that postoperative morbidity and mortality are related to co-morbidities rather than to the patients' age.[30,31] As an example of colorectal cancer surgery, we learned that the presence of at least two

significant co-morbidities has a substantial effect in patients older than 70 years, resulting in a mortality of 16.2% when compared with 8.6% in a younger cohort.[32,33] Emergency surgery even adds up the risks to 41% in patients aged over 80 years in the Dutch nationwide population-based study.[34] One-year postsurgical mortality was even 51.2% in patients aged 80 years and older in an English cohort, indicating that age was an independent determinant of mortality in risk adjusted regression analyses.[35]

Increasing age is associated with an increased risk of mortality.[34] Spot lights should be on preoperative conditions of fitness at advanced age such as 'frailty', age-related muscle loss (sarcopenia) and malnutrition.[36,37] Postoperative morbidity rates of adult patients are significantly higher in malnourished condition.[38] These topics indicate which elderly individual is more vulnerable to encounter adverse outcome and 'failure to rescue'. Hence, identifying 'frail' octogenarians is of utmost importance to acquire a realistic prognosis of cancer surgery. Instruments developed for this are unfortunately still time consuming and not very practical.

As a conclusion, age matters, but elderly patients can be operated upon with acceptable morbidity and mortality in elective setting. Moreover, elderly are expected to resume to a good quality of life after colorectal surgery also if receiving a permanent colostoma.[39,40]

Obstructive colon cancer

Population based data from the Netherlands revealed that 15% of colon cancers presented with obstructive symptoms [www.clinicalaudit.nl]. Patients may have only mild abdominal distension resolving after conservative management using enemas and laxatives, or may present with an acute abdomen because of blow-out of the caecum and fecal peritonitis. The treatment of obstructive colon cancer is associated with a relatively high morbidity and mortality.[41] In addition, obstruction impairs oncological outcome.[42]

For left-sided obstructing colon cancer, there is much debate on the most optimal treatment strategy. Given the 15% mortality rate associated with emergency surgery for colorectal cancer as demonstrated by recent population based data from England,[41] minimally invasive decompression in the acute setting followed by elective resection seems a more attractive approach. Before the introduction of the endoscopic stent, diverting colostomy was the alternative for acute resection, but associated with stoma related morbidity. In the intentionally curative setting, diverting colostomy was followed by elective resection with closing of the colostomy (2-stage procedure), or stoma closure in third instance (3-stage procedure). In the palliative setting, a diverting colostomy becomes often permanent with a negative impact on quality of life.

Diverting colostomy versus acute resection

The literature on diverting colostomy as a bridge to elective resection for obstructing left-sided colon cancer is scarce and only one randomized controlled trial (RCT) has been published. Kronborg et al., randomized 121 patients between 1978 and 1993, of which 58 underwent median laparotomy and colostomy followed by resection and anastomosis in second instance, and 63 underwent an acute Hartmann's procedure followed by restoration of continuity in second instance ($N = 56$) or acute resection with anastomosis ($N = 7$).[43] During follow-up (4 months–15 years), permanent colostomy was less often observed in patients undergoing staged resection (3/35 vs. 14/50, $p = 0.05$). No difference in postoperative complications, mortality or cancer specific survival was observed.

Stent versus emergency surgery

Much more studies on endoscopic stenting as bridge to surgery for obstructive colon cancer have been published compared to diverting colostomy. It seemed that the stent was going to resolve all problems related to the complicated acute resection and the need for multiple surgical procedures. Initial retrospective cohort studies were very promising.[44,45] Subsequently, RCTs comparing stent and acute resection were conducted to increase the level of evidence.

Of seven RCTs published in the literature after 2005 comparing endoscopic stenting with emergency surgery, three included only patients in the curative setting, three studies mostly in the curative setting and one study enrolled only palliative patients. Four of these seven RCTs prematurely stopped for the following reasons: more leakage after one-stage acute resection with anastomosis and colon lavage,[46] stent perforations ($N = 2$), technical failure of stent placement (53%),[47] and high complication rates in the stent groups of the remaining two trials.[48,49] The study of Sankararajay et al. was an interim analysis and has only been published as abstract.[50] Pooled technical success rate of stent placement in these trials was 112/155 patients (72%), ranging from 47% to 100% among the individual studies. Stent related perforations within 30 days were observed in three of six trials who reported data on this outcome measure: 2 (7%), 2 (20%) and 6 (13%) perforations.[47–49] The study on palliative treatment reported also long-term perforations in 4 patients (40%).[49] Two of the seven trials reported occult perforations that were identified during pathological examination of the resected specimen with a stent in place. The overall occult perforation rate in these 2 trials was 11/45 (24%).

Several meta-analyses have been published. Tan et al.[51] found no difference in in-hospital mortality, anastomotic leakage, and 30-day reoperation rates based on four RCTs.[46–48,52] Although early stoma rates were

significantly lower in the stent group, there was no significant difference in permanent stoma rates but a trend was observed in favour of the stent group. Based on three RCTs,[47,48,53] Cirocchi et al.[54] found also no significant differences in 30-day mortality, overall complication and permanent stoma rates. Sagar et al.[55] based the meta-analysis on 5 trials including one trial in the palliative setting.[48–50,52,56] A stent perforation rate of 5.9%, stent migration and obstruction rate of 2.1% each, similar 30-day mortality rate of 2.3% in both groups, and successful clinical relief of obstruction of 78% and 99% for stenting and emergency surgery were found respectively. Advantages of using a colonic stent as bridge to elective surgery consisted of lower mean hospital stay (11.5 vs. 17.2 days), shorter operating times (114 vs. 144 min), and less median blood loss (50 vs. 350 ml).

Stent versus diverting colostomy

Two RCTs compared stent with elective diverting colostomy in the palliative setting.[56–58] In the trial of Xinopoulos et al., 6 of 15 patients developed tumour ingrowth into the stent, which was treated by laser.[57] Since the stent was successful in relieving obstruction and prevention of stoma placement, it was concluded from these trials that a stent is the preferred technique in the palliative setting.

International debate on stenting

After the initial enthusiasm about colorectal stenting, this procedure has now become controversial due to serious complications of which perforation is the most important. Clinical application of colonic stenting varies tremendously in Europe. In the UK, stenting is considered standard of care by many surgeons who often do the procedure themselves. In contrast, stenting has been almost completely abandoned in France, Sweden, Norway, and the Netherlands. Moreover, publication bias supporting stenting makes literature difficult to interpret.

Stenting seems to have a place in the palliative setting if the life expectancy of the patient is restricted (less than 3 months). Of note, anti-angiogenic agents like bevacizumab have been associated with late perforations in the palliative setting.[59] The alternative treatment option, a diverting colostomy, has its stoma related morbidity. For the purpose of adequate decision making, acute CT staging is very important to determine loco-regional extent of the tumour and presence and degree of metastatic disease. Furthermore, free abdominal air due to for example cecal blow-out can be adequately identified by CT.

In the curative setting there are concerns about the oncological safety of stenting as bridge to elective surgery. If a perforation occurs during the stent procedure or afterwards, treatment is likely to be turned into a palliative setting. A recently published retrospective comparative study reported a significantly higher 5-year cancer-specific mortality after stenting compared to immediate surgery (48% vs. 21%).[60] The investigators did a more thorough pathological examination of specimens after stenting and found significantly more ulceration, perineural invasion and lymph node invasion compared to a matched control group of acute resection.[61]

The question, however, is whether the overall findings of stenting as bridge to surgery apply for different subgroups. Based on a systematic review of 54 non-randomized studies including 1198 patients, a Markov Chain Monte Carlo decision analysis was performed.[62] This model demonstrated that outcome after stent as bridge to surgery compared to emergency surgery depends on the success of the stenting procedure and the patients' underlying operative risk. Therefore, the elderly frail patients with a short stenosis that is technically considered to be a "stentable" lesion is probably a good candidate for a stent as bridge to surgery in the curative setting, rather than acute resection. In healthy patients (i.e. below 70 years of age without significant co-morbidities), acute resection should be considered as standard of care.

For patients not suitable for stenting and with a high operative risk, diverting colostomy is a suitable treatment option. This procedure does not have the disadvantages of a laparotomy in the acute setting. A diverting transverse colostomy as bridge to elective (laparoscopic) resection of the primary tumour, also referred to as a "blow hole", is not very popular among surgeons and there is almost no literature on this surgical approach.[63]

Finally, given the clinical problems associated with obstruction, early detection and treatment is of utmost importance. This may be reached by reducing symptom to diagnosis and symptom to treatment intervals.[64]

Principles of surgical anatomy

Surgical anatomy of the colon and rectum is defined by embryological planes. In colorectal cancer surgery three margins can be involved by tumour spread. The most well-known are the proximal and distal margins. Yet, the circumferential resection margin (CRM) is the most important due to the frequency of which it is invaded, its main impact and importance on outcome.[65–67] A clear CRM can be obtained by sharp dissection following embryological anatomical planes, which means separation of the visceral fascia (mesocolon and mesorectum) from the parietal planes (Toldt white line, Denonvillier and Waldeyer fascias).[68,69] This dissection should lead to a surgical specimen with an intact coverage, not only of the tissue over the tumour, but also of the main lymphatic drainage. Including the majority of regional lymph nodes, lymph vessels, and surrounding fat tissue lying within these mesos is essential in colorectal surgery.[68–70] In colon surgery, the so called mesocolic or mesenteric margin is defined by the adventitial soft tissue closest to the deepest penetration of the tumour.[71] This embryological knowledge has driven to

rediscover an old but forgotten technique; the Complete Mesocolic Excision with central vascular ligation.[70,72] Preoperative work-up with CT should try to evaluate this.

In rectal surgery, the mesorectal fascia (MRF)[73] is the relevant radial margin. The relationship of the tumour location anatomically to the MRF has emerged as one of the most powerful predictors of outcome.[74] In tumours located between the anal verge and the puborectal sling, the anal sphincters constitute the corresponding significant radial margin because the MRF does not extend past the puborectal sling.[65]

Preoperative work-up of rectal cancer should include T-stage of the tumour, location of pathologic lymph nodes, the relation to the MRF, to the pelvic floor and sphincters. Phased array MRI is the best tool for predicting MRF involvement; and the best cut-off distance for predicting the MRF involvement is described as 1 mm.[75]

If the MRF is involved, other surgical strategies should be employed which will be discussed in the paragraph surgery in locally advanced disease (beyond TME).

Phased array MRI is accurate in measuring the distance between the puborectal sling and the distal part of the tumour. This is important to define the height of the tumour to estimate whether a (low) anastomosis is feasible and recommendable.

The principal aim of surgical curative treatment is complete resection. Local recurrence is failure of complete local removal of the tumour. Therefore, the quality of the operative procedure performed by the individual surgeon represents one of the most important prognostic factors.[76,77] The CRM will be affected: if there is an involvement of the fascia within a properly dissected surgical plane or when bad quality surgery has been performed and the surgical plane is located inside the mesorectum. Therefore, digital photography of the pathology specimen and standardized pathological assessment of the resected specimen is crucial.[65]

Rectal cancer surgical considerations

Training TME and surgical standards

Before the 1990th local recurrence rate of rectal cancer was offensive high in many countries, and percentages of 20–45% are found in the literature.[78–82] Surgical technique in those days was regularly not standardized. Programs were initiated to improve rectal cancer care such as the Norwegian Rectal Cancer Project.[77,83,84] This project developed an educational 'hands on' training to properly teach surgeons, pathologists and radiologists the mesorectal excision, the anatomy of the rectum and the pathology of the tumour. Mesorectal excision is a precise and sharp dissection around the mesentery or mesorectal fat of the hind gut, which envelopes the entire mid rectum.[68,69] Several reports showed that if refinement of surgical technique is taught, local recurrence rates are much better.[77,83–86] Recently, the Spanish Rectal Cancer group showed that implementing a similar educational program as the Norwegian group is feasible in another country and they achieved a local recurrence rate of only 4.7%.[76]

Volume–outcome relationship for surgeons

Volume is another issue that has shown to improve patient outcome in colorectal cancer management, the higher the caseload, the better outcomes.[87–89] Furthermore, "bad providers" seem to miss quality standards for various outcome measures, both complications and oncological outcomes. Departments having high rates of anastomotic leakage and postoperative mortality, also have high rates of local recurrence and inferior long-term survival.[89]

Quality of life and sexual and urinary functioning

Early discovery and advances in surgical techniques alone or in combination with radiotherapy have increased the life expectancy of individuals with rectal cancer.[90,91] Especially in rectal cancer, the technique of total mesorectal resection (TME) has improved loco-regional relapse rate and is more sphincter and nerve saving. Cancer survivors need to live with the impact of the treatment on their quality of life and functioning. This frequently includes dealing with urinary and fecal incontinence or living with an ileo- or colostomy and sexual dysfunction.

Rectal cancer surgery and radiotherapy can have a negative impact on the pelvic nerves. According to recent Scandinavian studies, long-term functional problems are significantly increased among patients receiving neoadjuvant treatment compared to patients having surgery alone.[92–94] Fecal incontinence is reported by 15% of patients having surgery alone vs. 49% of patients having preoperative radiotherapy. Urgency is reported by 16% and 44%, and sanitary pads are needed by 13% and 52% of the same two groups. Nine or more daily bowel movements are reported by 3% vs. 19%, and urinary incontinence increases from 2% to 9% following radiotherapy. Dyspareunia is seen in 11% of patients having surgery alone vs. 35% for women also having radiotherapy, and erectile dysfunction score is reduced from 14 to 7 by radiotherapy. A restricted social life is reported by 7% of patients treated by surgery alone vs. 35% of patients treated by radiotherapy followed by surgery. Hip fracture happens among 1% of the patients after surgery alone vs. 5% following radiotherapy, and the rate of a second cancer is doubled by radiotherapy, from 4.3% to 9.5%.[95]

Pathology report

The quality of a surgical dissection is for an important part described by the pathologist. Minimum consensus, which is less than 70% but more than 50% agreement, was reached for the proposal that all forms of perforation, when identified at gross examination, should be considered

as pT4 because it creates uniformity in staging and it is relevant with regards to prognosis, although it is not according with the TNM classification. During the consensus meeting, it was agreed that all forms of perforations, iatrogenous or by advanced tumour stage, should be described if visible in the operative report and in the pathology report. Moderate consensus, more than 70% agreement and less than 80%, was achieved for the statement that patients with colon cancer and less than 10 nodes evaluated should be considered as high risk and could be eligible for adjuvant treatment. The same agreement was reported for the definition of high risk stage II colon cancer patients, i.e. advanced tumour stage (pT4), <10 lymph nodes analysed, lymphatic vessel invasion, poor tumour grading, extended tumour length, or tumour perforation.

Quality of surgery

Quality assurance in surgery is on the agenda's in many countries for quite some times now and has exerted huge effects of improvement of patient outcome measures such as mortality and survival. Registries, audits and training of surgical techniques mentioned before are able to save lives. Volume per surgeon in open and laparoscopic resection are issues every surgeon should take responsibility for, because these matter for the outcome of the patients. National and international initiatives that register data on patient, treatment and outcome are the key to improve surgical care.

TEM, RT and surgery

Transanal endoscopic microsurgery (TEM), a minimally invasive procedure, is indicated for removal of benign or premalignant rectal tumours and early stage rectal cancers (T1). A full thickness excision is performed from the rectal wall and leaves the mesorectum in situ. Benefits of a TEM procedure might be reducing the adverse effects of rectal cancer surgery; no abdominal scars, less sexual and urinary dysfunction, less diarrhoea, less surgical complications.[96] With emphasis, this is at a possible cost of loco-regional recurrence.[97]

Take into account possible lymph node metastasis (in pT1 approximately 8%) that are not treated when chosen for TEM and that TME surgery is recommended anyway when the pathology report reveals high risk features such as lymphovascular invasion, tumour stage more than T1sm2, poor differentiation grade or incomplete resection. Follow-up is recommended very frequently with endoscopy, CEA and additional imaging and/or biopsies in case of symptoms.

TEM and neoadjuvant treatment

Sometimes the rectal tumour has diminished to such an extent after chemoradiotherapy that it can be possible to remove it without major surgery. The most dramatic tumour reduction is when the tumour has completely gone and the patient can be put on a wait-and watch program. However, if there still is a remnant of the tumour which is seen at endoscopy there are no data supporting that those cases should be put in the wait-and-watch programme, but they should be offered surgery. The question is whether in those cases radical surgery or a local excision should be done. The evidence is very weak. Only one randomized trial has so far tested this hypothesis where 100 patients were randomly allocated to have TEM surgery or laparoscopic TME surgery after neoadjuvant chemoradiotherapy.[98] In that study no difference was seen in local recurrence rate or in overall survival or cancer specific survival, but an obvious benefit en QOL and morbidity in the local excision arm. That trial is heavily underpowered but gives us a hint that it might be possible that in patients with a modest complete downgrading after chemotherapy these patients may be suitable for local excision and not radical surgery. The risk taken is whether positive lymph nodes are left behind with a local excision. The positive effects are less morbidity to the patients. It is too early to start such treatment outside strict protocols, and before one can recommend such an approach this treatment algorithm has to be evaluated in larger randomized trials.

'Wait & watch'

Rectal cancer surgery is accompanied by substantial morbidity, and mortality after surgery remains. Therefore, an interesting question is if it is possible to avoid unnecessary resections. In patients with locally advanced T3/T4 tumours, preoperative chemoradiation can be used for downstaging, followed by curative surgery after a certain time interval to allow a response of the chemoradiation. In a review of phase II/III studies, the overall pathological complete response (pCR) was 13.5%.[99] Glynne-Jones et al. evaluated in a review a 'wait and see' policy after chemoradiation as treatment for rectal cancer.[100] Eighteen retrospective articles of Habr-Gama et al. and twelve non-Habr-Gama articles of which two were prospective were included. The Habr-Gama studies showed a low loco-regional recurrence rate of 4.3%, and survival rates that are comparable with survival rates of patients that had preoperative chemoradiation and curative resection with a pCR in the resection specimen.[101–103] A prospective study by Maas et al. showed comparable results.[104] In contrast, other retrospective studies showed much higher recurrence rates. Although the studies included in the review were very heterogeneous in diagnostic and treatment strategies, were not randomized, had small sizes and consisted of highly selected patients, it remains very interesting to develop a non-surgical approach for selected patients as an alternative to TME surgery.[100]

Personalized approach to locally advanced and locally recurrent rectal cancer (LARC & LRRC)

Unfortunately some patients do not fit well in this framework, more specifically patients with locally advanced and locally recurrent rectal cancer. If a primary rectal cancer breaches through the mesorectal fascia and infiltrates into the surrounding structures, like sacrum or piriformis muscle, or into the pelvic organs, it can be staged as a T4b tumour and is considered locally advanced (LARC). All locally recurrent rectal cancer (LRRC) patients may also be considered locally advanced. These locally recurrences originate in a tumour bed, which is not delineated anymore by an anatomical fascia, and easily involve more pelvic spaces. By their nature of involving different anatomical structures LARC and LRRC represent a very heterogeneous group of rectal tumours.

Consequences for the treatment

The objective of treatment of locally advanced or recurrent rectal cancer remains the same and is to achieve a complete radical R0 resection.[105] The required extent of the resection is more challenging. To achieve an R0 resection in these tumours, requires an 'en bloc' resection of the involved organs and structures. The variation in topographical locations determines the variety of the required surgical procedure.

Several factors influence the possibilities of achieving this goal. For example preoperative irradiation for a primary tumour may limit the possibilities when a local recurrence occurs. Fibrosis, desmoplastic reactions, chronic abscesses or even worse, anastomotic dehiscence, may all prevent easy access to the pelvis in LRRC patients, not only at the site of the tumour, but also during the surgical approach to the tumour. The most essential fact remains that after removal of the mesorectum within its enveloping fascia no natural border does contain the tumour to a specific anatomical volume, and all pelvic spaces lie wide open and are at risk of being involved even by a small recurrence. More or less T4b tumours present with similar challenges. Often these tumours are quite spacious especially in mucinous adenocarcinomas and prevent a standard surgical approach. Bottom line is, that both LARC and LRRC have a very heterogeneous presentation requiring much more different surgical solutions to achieve a radical en bloc resection than a mere abdomino-perineal excision or (low) anterior resection.[106] A more differentiate or even personalized approach is required.

Unlike in conventional rectal cancer, there is a more prominent role for PET-CT in the work-up of these patients. MRI cannot easily differentiate between fibrosis or desmoplastic reaction and tumour, like a PET can do.[107] Not only the diagnostic work-up is different, also the neoadjuvant treatment may have to be changed. Especially in patients with LRRC necessary downstaging may require an alternative approach. However, the most important difference regards the surgical procedure which is required to achieve a radical resection. It cannot be expected that a surgical team will ever require sufficient experience with these types of resections when confronted with these patients now and then in a regular practice. One of the important conclusions of the "Beyond TME Collaborative" (BTC) was that these patients should be recognized as high risk patients and should be referred to a specialized center.[108]

The "Beyond TME Collaborative" is a worldwide group of experts in the treatment of locally advanced and locally recurrent rectal cancer.[108] Many of the EURECCA experts also participate in the BTC. This expert group noted that it would be impossible to develop an evidence based standard guideline for LARC and LRRC patients. The reason for this is that it is impossible to design randomized controlled trial for this extremely heterogeneous group of patients. The worldwide lack of standardization would lead to a kind of treatment by chance. Some patients would be lucky and would be referred to an expertise center and some would face a nihilistic approach or even worse, ineffective but mutilating surgery. By inviting all the well-known experts in this field, who would combine their experience and would look at the scarce evidence present, and subsequently use the Delphi method to reach to a consensus document, it was hoped to provide a framework for the diagnostic work-up and treatment of LARC and LRRC patients. The final consensus document with its very important appendices was published recently in the BJS.[108] The primary goal of this consensus document was to decrease the inappropriate variance in practice in both non-specialist and specialist centers.

It may not come as a surprise, that the BTC consensus document statements are complimentary to the EURECCA consensus statements. Small differences do exist with regard to the various phases of diagnostic imaging and treatment of LARC and LRRC patients. Whereas the role of PET-CT is limited in the conventional work-up, it may have an added value in these advanced cases. In these cases, which require extended multivisceral resections, the a priori chance of occult metastases, which could be a definite contraindication for extended surgery, is higher. Furthermore, MRI has difficulties in differentiating between fibrosis and tumour. PET-CT, and possibly diffusion weighted MRI, may be used for this differentiation.[109] The role of high resolution CT for evaluation of the lungs remains undisputed, albeit that this modality will reveal many more nonspecific nodules, which are only metastases in a limited percentage, but they may inadvertently confuse decision making.[110] CT or ultrasound guided fine needle aspiration of suspected lesions in the pelvis have a role in work-up.

Once the diagnosis has been made and the extent of the tumour is defined, downstaging becomes a very important issue. Reducing the field for the resection will translate into a smaller procedure with potentially less functional

deficit and subsequently better quality of life. Responders to neoadjuvant treatment will also have an improved oncological outcome.

Many combinations of neoadjuvant treatment have been investigated. Combinations of preoperative (chemo-) radiation with systemic courses of chemotherapy are under consideration. Especially since a recent phase 2 study revealed that systemic therapy has a strong capability to downstage the primary tumour in stage IV rectal cancer. However, many of these schemes have been investigated in conventional rectal cancer patients, who are unlikely to benefit from these intensified schemes and therefore failed to demonstrate a better outcome. Nonetheless, effectiveness of these approaches in T4b and locally recurrent rectal cancer remains to be evaluated.[111] Especially in previously irradiated locally recurrent rectal cancer patients, downstaging may be difficult to achieve and the use of systemic therapy in combination with an even more disputed limited re-irradiation should be considered.[112] The same is true for locally advanced tumours presenting as bulky disease.

In LARC and LRRC patients, combinations of neoadjuvant treatment allow to select responders from non-responders and potentially incurable patients with tumour progression under treatment, and who will not be cured by surgery, or even worse, who will also needlessly suffer from the morbidity of mutilating surgery.

The worldwide panel of specialists of the BTC agreed unanimously that these patients should be treated in super specialist expert centers, and that a referral system should be implemented to secure access of each individual patient to the most optimal care.

The use of intraoperative radiotherapy (IORT) should seriously be considered as a technique to overcome dose limitations for external beam radiotherapy in selected cases.[113] Intraoperative radiotherapy, either as high dose rate brachytherapy using the flap technique or electron beam radiotherapy with a linear accelerator as a boost in combination with preoperative radiotherapy, can deliver a local dose up to 90–100 Gy, at a specific small high risk volume. In selected cases the infield (re)recurrence rate may be reduced with 50%.[114] T4b and LRRC are relatively rare and very heterogeneous representations of rectal cancer. Without consensus initiatives like EURECCA and BTC, wide variation in diagnostic work-up and treatment would persist and subsequently patients would remain at risk to receive inappropriate treatment.

Surgery in stage IV disease

Systematically spread cancer is normally not curable with local treatments as surgery, ablation or radiation therapy. Still for some cancer types, e.g. colon and rectum cancer, the systemic spread can be defined to a limited number of organs and also the lesions can be counted. We cannot biologically explain why some cancer types but not others tend to have a limited metastatic distribution and why resection or ablation of visible lesions in fact leads to significant long-term survival. For colon and rectum cancer a number of retrospective studies during the last centuries have shown that a subpopulation of patients with limited metastatic disease can be cured with surgical resection. Liver resection for metastases leads to five year survival in the interval of 30%–50% depending on the indications.[115–120] The indications for curative intended surgery can be narrowed into several categories and the result of the experts votes serves as base for the strength of consensus. In general, the decision whether metastatic disease is resectable or not, and how it should be treated, is best taken in a tumour board including a liver surgeon.

Liver metastases are common in colon and rectum cancer both when the primary tumour is detected (synchronous) and after a recurrence free interval (metachronous). Earlier it was thought that synchronous liver metastases and bilobar lesions indicated worse prognosis, but this is not the view today. Patients who had a liver resection for many metastases have worse prognosis than patients with a single metastasis, but five or more metastases is not a contraindication to surgery. Today liver resection is indicated if >30% of functional liver parenchyma can be preserved, portal vein and hepatic artery inflow and at least one hepatic vein can be spared and that a R0 resection is possible. The surgical technique has changed from mainly lobe resections to segmental or atypical resections, the margin should preferably be 1 cm, but 4 mm is OK, and if necessary 1 mm is accepted,[121,122] and ablative techniques are frequently used in addition to resection.

Synchronous liver metastases

There is large consensus that these patients can be treated in a potentially curative fashion. The treatment strategy, preferably taken after discussion in a tumour board, for synchronous oligometastatic colon or rectal cancer should be based on the possibility to achieve R0-resection, either initially or after induction treatment for systemic disease and primary tumour. When the liver metastases are resected before or at the same time as the primary tumour, there is no data whether this should be without preoperative chemotherapy or with chemotherapy. There is limited but convincing evidence that a liver first reversed management can be performed before surgery of the primary tumour.[123,124] The recommendation is that the total time pre- and postoperative chemotherapy should be given is 6 months for all cases of resected synchronous liver metastases.

In case of potentially resectable or initially unresectable liver metastases the most active available induction treatment should be given. A considerable number of patients will become candidates for resection and the principles are the same as for initially resectable metastases. If the tumours after two or three months of treatment still are not resectable, the same schedule can be continued in case of some tumour shrinkage or the treatment can be changed.

These decisions are best taken in a tumour board just as the decision that liver tumours will never become resectable. The numbers of cases with liver metastases that are resectable are underestimated if a liver surgeon is not being involved in the decision. Resection of liver lesions is preferred to ablation, but in case of contraindication for surgery, radiofrequency ablation (maximum diameter 3–4 cm) or stereotactic body radiation therapy (maximum diameter 4–5 cm) can be considered after a tumour board discussion. There is no evidence that the choice of resection technique and whether it is performed open or laparoscopic is of any major importance for outcome.

Other metastatic sites

Other metastatic sites where curative intended surgery is indicated are lungs, lymph nodes and peritoneum. Lung metastases are resected if they are limited to a few and located in one lung lobe. Factors that might influence survival after resection for lung metastases are prolonged disease free interval between surgery of primary tumour and lung metastases, normal pre-thoracotomy CEA, absence of thoracic node involvement, and single pulmonary lesion. Data from registries and retrospective series show a five year survival of 27–68%.[125] Many patients also receive neoadjuvant or adjuvant chemotherapy for a total time of 6 months. For distant lymph node metastases there is an indication for resection of metastatic nodes in the hepatoduodenal ligament, but not for coelic or para-aortic nodes.[126]

It is estimated that 5% of patients with colon or rectal cancer have isolated peritoneal carcinomatosis[127] and approximately half of these might be candidates for cytoreductive surgery (CRS).[128] The difficulty is to identify patients with limited disease so that surgical resection leaving no residual disease behind is possible. It demands experience both to diagnose the right cases for surgery and to do CRS. The procedure should be centralized to a few centers and in experienced hands CRS with hyperthermic intraoperative peritoneal chemotherapy (HIPEC) is superior to systemic fluorouracil and leucovorin chemotherapy. In the only randomized controlled trial by Zoetmulder and colleagues[129] 105 patients were randomized to CRS + HIPEC and postoperative systemic chemotherapy versus only systemic chemotherapy and median survival was significantly better in the surgery arm (22 vs. 13 months), but the advantage was only seen in the minority of patients where no residual disease was left behind. A few smaller cohort studies of limited evidence value do support a survival benefit. Five year survival is around thirty percent.[130] CRS + HIPEC has not been challenged in studies where more efficient chemotherapy combinations are used. Postoperative morbidity after CRS + HIPEC is considerable with approximately one third of patients experiencing major complications, and postoperative mortality is 0–8%.[129] The voting process lead to full consensus that CRS + HIPEC is indicated in patients with good general health status, limited intraperitoneal tumour dissemination (peritoneal cancer index, PCI <20), limited bowel disease, and no extra-abdominal metastases.

Metachronous liver metastases

For initially resectable cases of metachronous liver metastases the debate is whether patients should receive preoperative or postoperative chemotherapy. Randomized studies to answer this question are few and the largest study EORTC 40983[131] included 364 patients and showed a significantly prolonged progression free survival (PFS) of 7 months in the subpopulation who had surgery and also neoadjuvant FOLFOX4 chemotherapy. The study failed to show this in the intention to treat (ITT) population as well as it did not show significantly improved three year overall survival.[132] The practice to give 6 months of neoadjuvant/adjuvant chemotherapy is therefore much an extrapolation of larger studies where adjuvant treatment has been given to patients with stage III colon or rectum cancer. Chemotherapy should prevent liver and/or extrahepatic recurrence and from that perspective that size and number of liver metastases should not make any difference. For single liver metastases <2 cm diameter there was minimum consensus whether these patients could be operated upfront and then receive 6 months of chemotherapy. A liver resection only approach has some support from retrospective data analyses where patients with resected single liver metastases <5 cm had the same survival whether they had chemotherapy or not.[133]

There was moderate consensus in the voting for upfront surgery in patients with large or multiple liver metastases suitable for hemihepatectomy or extended hemihepatectomy if enough remnant liver is left behind for regeneration. There was also large consensus for the alternative that these patients could have three months of neoadjuvant chemotherapy before surgery and that both those who had upfront surgery or neoadjuvant chemotherapy should have a total of 6 months of chemotherapy.

A known bad predictive factor is preoperative progress on chemotherapy with <10% five years survival[133] but this does not always exclude resection. There was large consensus among the voting experts that in case of primary progression during preoperative chemotherapy, after discussion in a tumour board, best available salvage treatment may be preferred instead of liver resection.

For borderline R0 resectable cases there was large consensus that patients could either have portal ligation/embolization before resection and then 6 months of chemotherapy or have the most active available chemotherapy for a limited time of 3–6 months for downsizing before resection and then receive postoperative chemotherapy up to a total time of 6 months. It is important that frequent liver imaging is performed during treatment as radiographic complete remission of lesions before surgery should be avoided. The area of the lesion needs to be identified and resected or ablated. A vast majority of radiographic

complete responses of liver metastases are no true complete responses and will recur if left in place.[134]

Discussion of the consensus diagnostics and therapies in colon and rectal cancer

The EURECCA consensus on colon and rectal cancer diagnostics and therapies is a step towards unifying treatment standards for colon and rectal cancer in Europe. Defining minimal requirements for cancer management of colon and rectal cancer is thought to positively interact with healthcare providers and politicians in all of Europe. The consensus should be applicable in entire Europe. The experts did recognize existing economical differences[135] (i.e. annual expenses for health ranging in 2010 after correction for purchasing power parity from $995 in Poland to $4607 for Norway). The proposed solutions should not lower good standards achieved in some countries, otherwise it should be practicable in every health system. It should be stated that the majority of the experts came from Nordic and Western European countries, and most publications used for reference originates from these countries, creating publication bias. On the other hand, published data from other parts of Europe is limited. There is an urgent need for expanding quality projects in these countries[136,137] and EURECCA supports this process.[138]

The consensus document is thought as guidance and standardizing treatment and is not a cookbook, as stated by Sackett.[139] In the consensus process different options reaching from literature overview to accurate normative recommendations were presented. The used Delphi process harbours some limitations; concerning the level of consensus (percentual level of agreement defined as consence), feedback between the rounds and running of the online voting. The final version, which is quite extensive, gives no information whether an expert has denied a given a statement i.e. as overtreatment or undertreatment. The consensus document gives recommendations about diagnostics and treatments for colon and rectal cancer patients to the treating physician, but reserves the final decision to his/her discretion.

As mentioned before, the novum of this consensus meeting in comparison to previous versions[140] is the inclusion of colon cancer. The focus on improving outcome of rectal cancer management might have been one of the reasons rectal cancer survival got better in time.[1] The question is, if we focus more on quality in colon cancer management can outcome of colon cancer be improved as well?[90]

To report on the outcome of the multidisciplinary consensus conference, we would like to highlight some of the recommendations; the conference decided to draw precise pathways for minimal requirements of preoperative staging and to recommend the use of standardized protocol for pathological evaluation of the specimen.[141,142] The implementation of both gives a chance to compare surgical quality and opens the door to more precise and individualized decision making regarding the need of adjuvant/neoadjuvant treatment. Evaluation of a possible R0 situation obtained by meticulous surgery alone plays an important role, both for primary tumours and for metastatic disease. The conference has not decided to recommend the use of one version of the TNM UICC-classification, being aware of existing limitations and national obligations, version used is recommended to be added to the pathology report. A comparison of survival between countries and project using different versions is furthermore not possible.[143] It have to be mentioned that costs of surgery[144] is only a neglectable fraction of the entire therapy costs[145] so the industrial influence regarding therapeutical and research options have to be considered.

The consensus document did not deal with the patient's quality of life (QOL). Patient organization representative were invited to collaborate to interact between consensus outcomes and delivering quality for the patient. With increasing patients involvement in setting of the treatment standards an inclusion of QOL-issues can be expected for the next conference. The consensus document is being converted into a patient summary to inform patients about this consensus.

During the consensus conference the benefits and troubles of laparoscopy were discussed taking into account the limitations of the technique and some reports of worse results in the converted patients.[146] The experts stressed the necessity of experience and learning curve, as well as a difference between preemptive and reactive conversion, however precise definitions still have to be set. There is a high level of evidence to support laparoscopic resection of colorectal cancer, but this should only be done after adequate patient selection by an experienced surgeon. It must be discouraged to perform laparoscopic surgery in departments, where the total number of patients is lower than the learning curve.

The consensus document emphases the need of MDT. Unfortunately the document as well as available literature does not provide a definition of an MDT. Is every group of different specialized oncology related physicians a tumour board? Recently published studies describe limited impact of MDT-meetings[147] and do question their cost-effectiveness.[148] It can be expected, that the future will further replace the MDT by a requirement of sufficient multidisciplinary responsibility for therapeutic decisions, without requiring a special gremium or form of communication. Some dissimilarities in the approach do result from the organizational differences of health systems in different countries. For example, in some countries surgery for rectal cancer and liver metastases is performed by the same surgeon, in some other by different teams or even departments.

During the consensus process, it was confirmed that surgery remains the key treatment option for colon and rectal cancer. To keep this consensus 'up-to-date' will remain a dynamic process; further scientific developments will

substantiate the present recommendations. For the future a diversity of EURECCA-CC3 fruits can be expected, some of them leading towards precised treatment option, some others provide expert overview of published evidence, others creating research platform for open scenarios. The present consensus is a basis for more differentiated and tailored treatment. EURECCA[121] remains a platform of cooperation, where different health systems, projects, attitudes can meet and provide improvement for our patients, despite of the part of Europe where they live.

Realizing a framework for a standardized approach enables to fine-tune the treatment to the specific needs of an individual patient. Equally important is to realize that consensus represents knowledge from the past and that many questions still have to be resolved in the future. In order to do so data have to be collected preferably in a prospective way in registries. Only with the help of new data consensus can be kept up-to-date.

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