Quality assurance in surgical oncology

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11 General discussion and summary

GENERAL DISCUSSION

Gastric cancer

In 2002, 933,900 cases of gastric cancer were diagnosed world wide (http://info.cancerresearchuk.org/cancerstats/). Gastric cancer ranks second after lung cancer when it comes to cancer mortality: there are 700,300 gastric cancer deaths per year. Treatment is based on surgical resection of the tumour. In case of localised disease, surgical resection offers favourable survival rates. The problem is however that localised disease is rare in Western countries: only in case of advanced stage, signs and symptoms may indicate the likelihood of gastric cancer. Furthermore, mass screening programs that are helpful in diagnosing early stage are successfully employed in Japan, but are not common in Europe or the United States.

Surgery

Apart from stage disease, the quality and extent of surgery is a prognostic factor as well. In Japan (as much as 19% of all malignancies are gastric cancers), surgery does not only involve tumour resection. Extended lymph node dissection is performed on a routine basis as well. The extent of lymphadenectomy focuses on the main question: are the lymph nodes the tumour is draining to merely *indicators* or also *governors* of disease? In other words: does lymphadenectomy only serve staging purposes (opinion in Western countries) or has it also a therapeutical goal (reducing the likelihood of distant spread, [1-4]opinion in the Eastern Asia)? To answer this question, several randomised trials have been performed. Remarkably, in Japan no prospective randomised trial was ever performed to substantiate their own practise: convinced of the benefits of D2 dissection, setting up such trial has always been considered unethical by both patients and doctors. The two large European trials with adequate design, power and execution, were the British MRC[5,6] and the Dutch Gastric Cancer D1D2 trial[4,7,8]. Both trials failed to show any benefit from extended surgery. In the editorial accompanying Henk Hartgrink's final report on the Dutch D1D2 trial, Petrelli[9] concluded that the debate on the benefits of D2 dissection is over: there is no survival benefit of extended surgery after a median follow-up 11 years, and therefore no reason perform this kind of surgery on Western gastric cancer patients ("it's time to move on"). However, Petrelli's conclusion might be premature: postoperative morbidity and mortality of D2 dissection was considerable in both European trials and might have obscured a survival benefit of extended surgery. Indeed, subgroup analyses from the D1D2 trial show improved survival in patients who were assigned to D2 dissection and did not undergo organ resection. (During trial accrual, resection of spleen and pancreatic tail was not only preformed in case of organ involvement. It was also performed assuming that organ resection was necessary in order to achieve adequate nodal clearance (stations 10 and 11) in case of proximal gastric cancer). More recent reports show that organ preservation techniques can safely performed in Western patients, with low morbidity and mortality without compromising the extent of lymph node dissection.[10-14] Moreover, recently

the first prospective randomised trial was published showing a survival benefit of extended lymph node dissection: patients undergoing D3 gastrectomy had better 5 year overall survival rates than patients who were treated with D1 dissection. (59.5% vs. 53.6%, P = 0.041).[15] These interesting results were obtained in a single-center study, indicating that high-volume surgery in experienced centers might be an explanatory factor. Moreover, there is another subset of patients that benefit from D2 dissection: subgroup analyses from the D1D2 trial indicate a trend for better survival in N2 patients after a D2 dissection (lymph nodes are probably not only indicators but also governors of disease). It is likely that performing a D1 dissection without splenectomy and resection of the pancreatic tail, together with dissection of at least 15 nodes (a so-called over D1 (D1+) resection) results in better outcome.[16]

Another way of reducing overall morbidity and mortality is to tailor surgery to the individual gastric cancer patient. It is known from the D1D2 trial that patients older than 70 years of age, subjected to D2 dissection are more likely to suffer from postoperative complications.[4] Performing this kind of extended surgery in the elderly seems inadvisable.

A final and promising way of tailoring surgery involves resecting only those lymph nodes that are most likely to be involved by tumour. Prediction of nodal involvement by preoperative imaging has limited value. The concept of the Maruyama Index of Unresected Disease[17,18] (MI, see Chapter 3) may offer new opportunities: by collecting individualised patient and tumour characteristics prior surgery, the chance of nodal involvement of the D1 and D2 stations can be predicted by comparing these individual data to a large database of close to 4,000 Japanese gastric cancer patients. In this manner, unnecessary lymphadenectomy of uninvolved lymph nodes is prevented, thus reducing the likelihood of postoperative complications. The value of the MI has been established retrospectively in both the US Intergroup trial 0116[19] and the Dutch Gastric Cancer trial[18]: performing individualised "low-Maruyama-index-surgery" is probably better than dissecting the complete N2 echelon in every gastric cancer patient; postoperative complications are reduced and long term survival improves. Of course, it is premature to introduce the Maruyama concept before testing it in a prospective fashion. The newly designed CRITICS study (see later) offers the opportunity.

(Neo-)adjuvant treatment

Because the results of surgery alone are poor in case of locally advanced disease (i.e. extension through the gastric wall and involvement of peri-gastric nodes), attempts have been made to improve treatment outcome applying adjunctive treatment regimens. In contrast to colon cancer, adjuvant chemotherapy has not shown to be effective.[20-23] The addition of radiotherapy however (external-beam radiation delivered to the site of surgery and its draining lymph nodes) to fluorouracil and leucovorin after surgery is beneficial: the US SWOG trial showed that patients after multi-modality treatment had better median survival than patients treated with surgery alone (36 vs. 27 months, P = 0.005).[24] Also disease-free survival was superior (30 vs. 19 months, P<0.001). This trial was criticised on some points however,

the most important one being the fact that the majority of the patients (54%) had not even undergone a resection of the peri-gastric nodes (D1 level). The important confounding role of surgery was stressed earlier, and keeping this in mind, the question whether postoperative chemoradiation is of any value after optimal surgery remains largely unanswered. There are however some reports from non-randomised studies that adjuvant chemoradiotherapy in D2-resected gastric-cancer patients is tolerable[25] and can prolong survival and decrease recurrence.[26]

Another way of adjuvant treatment concerns peri-operative treatment. Theoretical advantages of preoperative treatment include increasing the chances for curative resection and relief from tumour–related symptoms, both through the mechanism of downstaging. Moreover, tumour response to chemotherapy can be determined. The British MRC trial tested in a prospective randomised trial whether peri-operative epirubicin, cisplatin and infused fluorouracil (ECF) could improve overall survival in patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus.[27] Rates of postoperative complications did not differ between the perioperative-chemotherapy group and the surgery alone group (46 percent and 45 percent, respectively), neither did the numbers of deaths within 30 days after surgery. With a median follow-up of four years, the perioperative-chemotherapy group had a higher likelihood of overall survival (hazard ratio for death, 0.75; P=0.009; five-year survival rate, 36 percent vs. 23 percent). Interestingly, the resected tumors were significantly smaller (median size 3 cm vs. 5 cm, P<0.001) and less advanced in the perioperative-chemotherapy group (proportion T1/T2 tumours 52% vs. 37%, P = 0.002, proportion N0/N1 disease 84% vs. 71%, P = 0.01). These findings favour preoperative treatment considering the difficulty to achieve curative resection in case of locally advanced disease (a patient category often encountered in Western countries). A disadvantage of infusional fluorouracil however, is the implantation of central venous catheter devices and the use of portable infusion pumps that bare the risk of complications such as thrombosis and wound infection. An alternative might be capecitabine, a prodrug and oral analogue of 5-FU that is believed to mimic continuous infusion of 5-FU. Capecitabine has demonstrated to be equally effective in tumor control and to be less toxic than intravenous 5-FU in patients with stage III and IV colon cancer.[28-30]

Data from the well designed MAGIC and SWOG/Intergroup studies raise the important question whether postoperative chemoradiotherapy improves survival and/or locoregional control in patients that receive neoadjuvant chemotherapy followed by a D1+ gastric resection. The recently developed CRITICS trial (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach, leading group Dutch Colorectal Cancer Group) randomises gastric cancer patients between 2 arms: ***1***. 3 courses of ECC chemotherapy prior to D1+ surgery followed by 3 additional ECC courses or ***2***. 3 courses of ECC chemotherapy prior to D1+ surgery followed chemoradiotherapy (45 Gy in 25 fractions plus capecitabin and cisplatin). Primary endpoint is overall survival. The trial is to be launched in 2007.

A final comment needs to be made on the role of sentinel node biopsy (SNB) and the clinical relevance of minimal residual disease (MRD) in gastric cancer patients. SNB, a concept pioneered by Morton et al.[31] in melanoma patients, has gained wide acceptance in the treatment of breast cancer patients: analysis of the sentinel node is used to predict the presence of metastasis in the corresponding nodal basin. In this manner, morbidity of unnecessary lymph node dissection is reduced without compromising locoregional control. To avoid inaccurate mapping, SNB should only be performed in early gastric cancer lesions: distortion of lymphatic pathways in locally advanced disease hinders reliable mapping. Japanese data show encouraging data, although the rate of accurate detection might be low for large tumours.[32,33] The fact that results in Western patients are less favourable is probably due to the more advanced stages of disease diagnosed in the West.

As mentioned before, disease recurrence is a major problem in gastric cancer patients. The current method for staging in gastric cancer is insufficient: not only are often too few lymph nodes removed leading to systematic understaging, also routine investigation of the removed nodes applying hematoxylin and eosin staining may not be accurate enough. To illustrate this inaccuracy, even after a complete tumor resection many patients who are considered to be node-negative suffer from disease recurrence. Searching for occult tumour cells (OTC) in these lymph nodes may identify this high-risk subset of patients. OTC comprise micrometastases with its size being more than 0.2 mm but less than 2.0 mm, and isolated tumor cells (size less than 0.2 mm). A recent case-control study by Doekhie et al.[34] showed that, although identification of OTC is technically possible, it can not predict disease recurrence. This is line with Japanese data that showed that the presence of immunohistochemically detected micrometastases in the regional lymph nodes did not affect the survival of pT2N0M0 gastric cancer patients who had undergone gastrectomy with D2 lymph node dissection.[35] The number of lymph nodes removed may serve as a more reliable predictor, stressing again that lymph node dissection has therapeutical value.[36]

RECTAL CANCER

In 2002, 1,023,200 patients were diagnosed with colorectal cancer worldwide (http://info.cancerresearchuk.org/cancerstats/). In Europe 11% of all cancer cases were bowel malignancies. It is the fourth most common cause of death from cancer worldwide accounting for 8% of all deaths from cancer. There have been steady increases worldwide in the numbers of people being diagnosed with bowel cancer over the last 25 years. Approximately one third of the colorectal cancers are rectal cancers.

As for gastric cancer, local recurrence is important issue for concern. Again, well-performed surgery is an important prognostic variable. It is increasingly acknowledged that local failure is more a matter of surgical technique rather than of aggressive biological tumour behavior.

Incomplete tumour resection with involvement of the circumferential resection margin by tumour and/or lymph nodes is the most important risk factor for local recurrence. The importance of complete resection is stressed by the fact that postoperative radiotherapy is not effective in case of irradical resection and therefore does not compensate for low-quality surgery.[37] This emphasizes the need for precise staging during the initial work-up for each rectal cancer patient. By accurate MR imaging, tumours can be classified according to the risk or local recurrence. Involvement of the mesorectal fascia calls for prolonged irradiation prior to surgery, leading to downstaging and –sizing, facilitating curative (R0) resection.

The benefits of short term preoperative radiotherapy (5x5 Gy)

The Swedish rectal Cancer Trial showed that 5x5 Gy followed by conventional surgery of operable surgery increased both local control and overall survival[38], also in the long run at a median follow-up of 13 years.[39] The efficacy of this regimen in TME treated patients was unknown until the early data of the TME trial were released: at a median follow-up of 2 years, local recurrence rate was lower in irradiated patient (2.4% vs. 8.2%, P<0.001).[40] There was however no effect on overall survival, hypothetically due to the rather short period of follow-up. With a median follow up of 6 years, irradiated patients still have significant lower recurrence risk compared to non-irradiated patient. (5.6% vs. 10.9%, P<0.001), chapter 8). The benefits of preventing local failure need to be stressed: intractable pain, incontinence due to sphincter ingrowth and rectal blood loss are prevented in many rectal cancer patients. In this respect 5x5 Gy is a valuable regimen. Moreover, the short term adverse effects of this radiotherapy are only minor, although perineal wound dehiscence after irradiating the perineum is a matter of concern.[41] On the long run however, fecal incontinence occurs more often in irradiated patients: 62% vs. 38%, P < 0.001 (chapter 7).[42] Moreover, satisfaction with bowel function is significantly lower and the impact of bowel dysfunction on daily activities was greater in irradiated patients compared to patients who underwent TME alone. This should prompt the medical community to tailor radiotherapy to those patients that are most likely to benefit from it. Not every rectal cancer patients has equal benefit from radiotherapy: the efficacy depends partly on the height of the rectal tumour. Therefore, it is tempting to perform subgroup analyses from the TME trial on tumour height in order to narrow the indications for 5x5 Gy. Caution is warranted: statistical power is often insufficient to detect clinical relevant differences. Furthermore, daily practice tells us that it is difficult to determine exact tumour position prior to surgery: discrepancies between endoscopy findings, CT/MRI imaging and intra-operative findings are not uncommon. Nevertheless, one may wonder about the implications of these analyses for rectal cancer treatment. Subgroup analyses do provide a degree of evidence, especially when the analyses are derived from the largest study so far on TME treated patients. Local failure after treatment of proximal tumours is relatively rare, making the number of patients needed to irradiate in order to prevent one local recurrence substantial. Moreover, the difference in local recurrence rate between the two randomisation

arms is non-significant (3.7% vs. 6.2%, P=0.122). For low-lying rectal cancers there is neither any significant effect of radiotherapy (10.7% vs. 12.0%, P = 0.578). An import confounding factor in distal rectal cancers is the rate of CRM involvement. As it appears from the TME trial, APR patients have undergone more often irradical resection than patients treated with anterior resection (26.5% v 12.6%, P < .001). Also, survival is substantial lower (38.5% v 57.6%, P = .008).[43] This is in line with a retrospective series from Leeds involving 190 APR and 371 AR patients, local recurrence was higher in case of APR (22.3% versus 13.5%, P = 0.002), overall survival lower (52.3% vs. 65.8%, P = 0.003).[44] Even after introduction of TME the incidence of CRM involvement in the APR group (41%) was much higher than in the AR group (12%) (P = 0.006). Finally, the Norwegian Rectal Cancer Group stipulated the same problem: in their prospective observational cohort study involving 2,136 patients with rectal cancer within 12 cm of the anal verge, 10 percent local recurrence after anterior resection and 15 percent after abdominoperineal resection was seen (P=0.008).[45]

Future challenges in rectal cancer treatment

Establishing resection without involved margins

Preoperative imaging with the aim to distinct operable from locally advanced disease is crucial. MRI scanning is the only reliable tool to assess mesorectal fascia involvement and should be done in each rectal cancer patient.[46] Of course, scanning a patient is not enough, gaining the radiological expertise to interpret the images is important as well. In case of suspected mesorectal fascia involvement, 5x5 Gy is not a good option. Hypofractioned preoperative radiotherapy followed by immediate surgery does not lead to downsizing[47] and does therefore not facilitate complete resection. Prolonged irradiation (25x2Gy) followed by surgery carried out 4-8 weeks following the completion of radiotherapy, reduces tumour size and therefore increases the chances for radical resection. According to several phase II studies[48-50] the addition of continuous infusion fluorouracil (FU) chemotherapy to external-beam radiation therapy potentates this downsizing and –staging effect. The addition of oxaliplatin to intravenous continuous infusion FU and radiotherapy for patients with locally advanced rectal cancer may be associated with even a higher pathologic complete response rate[51] up to 25%, but is associated with more acute toxicity than when FU is used alone.[52] Apart from acute side effects, late morbidity should be a matter of concern as well. In chapter 7 we showed the detrimental long-term effect of 5x5 Gy on bowel function.[53] The impact of prolonged chemoradiation is probably substantial as well, but still needs to be clarified.

APR patients constitute a separate category of patients; in the TME trial CRM involvement was unacceptable high (26.5%) and tumour perforation occurred frequently (13.7%)[54] The difficulty to obtain margins in distal lesions is understandable: when the mesorectal plane is followed completely down onto the sphincter apparatus, the risk of involved margins increases as the mesorectum is a only a thin structure when it closes into the sphincters.

This "coning in" into the tumour is prevented when the perineal phase is commenced earlier during rectal cancer surgery: by performing a cylindrical resection with removing the levator muscles en bloc, the risk of inadvertent perforation due to excessive manipulation during the abdominal phase is reduced. This radical resection may lead to less margin involvement but leaves a substantial defect that calls for closure using for example myocutaneous flaps in order to facilitate wound healing.[55-58]

Minimising the morbidity from rectal cancer treatment

TME offers the opportunity to work under close vision of nerves that are important for bladder and sexual function. Yet, there is still room for further improvement considering the degree of dysfunction that many patients report, even if they did not undergo radiotherapy. Although rectal cancer surgery may inevitably cause a certain level of dysfunction, all efforts should be directed towards optimal identification and preservation of important nerve structures. This might imply further training of surgeons in order to obtain maximum exposure of the operative field. We have to keep in mind however that bowel, bladder and sexual dysfunction is partly physiological in the elderly and therefore cannot be ascribed solely to the detrimental effects of rectal cancer treatment.

In contrast to (neo-)adjuvant treatment surgery is the mainstay of cure of rectal cancer, making a certain level of side effects acceptable. Short term preoperative radiotherapy however is responsible for "only" a relatively small, but statistically significant reduction in local recurrence risk compared to surgery.(chapter 8) Considering the severe symptoms that accompany local failure the administration of preoperative radiotherapy seems justified. Moreover, it has to be stressed that local recurrence was chosen as primary endpoint of he TME trial, and not overall survival. The fact however, that there is hardly any effect of radiotherapy on overall survival at a median follow-up of 6 years (63.5% vs. 64.2%, P=0.260), raises the question whether every rectal cancer patient should be offered this toxic radiotherapy regimen. As we know from subgroup analyses from the TME trial, local recurrences are relatively rare when rectal cancer is located more than 10 centimeters from the anal verge. One could argue not to irradiate these patients, especially when it concerns (elderly) patients with already moderate bowel function prior to surgery: fecal incontinence is considerable in irradiated patients, even when it concerns proximal cancer. The impact of bowel dysfunction on daily activities and quality of life should be counterbalanced at the reduction in local recurrence risk. One has to be bare in mind however that accurate determination of tumour height is crucial. This implies that there is a need for standardizing endoscopy. When in doubt a soluble water-enema might give valuable information.

Another category patients that are possibly overtreated by 5x5 Gy are patients with early (stage I, pT1/2N0) rectal cancers. Again from subgroup analyses of the TME trial, we know that local recurrence is extremely rare and the impact of radiotherapy is non-significant (0.4% vs. 1.7%, P=0.091). An absolute difference of only 1.3% seems not enough to irradiate

every stage I rectal cancer patient. The problem is however that accurate diagnosis of early lesions prior to treatment is difficult.[59] Therefore, it is difficult during pre-treatment work-up to estimate the risk of local failure and the possible benefits of radiotherapy. Not only radiotherapy, but also major surgery might imply overtreatment for early lesions. It is known that lymph node metastases are seldomly engaged in this subset of rectal cancers indicating that lymphadenectomy serves hardly therapeutical or staging purposes. By performing local excision of early lesions the morbidity of laparotomy is avoided. This would imply a major step in reducing late morbidity as a large proportion of long-term dysfunction can be ascribed to TME surgery, and not to radiotherapy. Local excision of even pT1 tumours may however be associated with unacceptable high local recurrence rates up to 26%.[60] Ending up with a local failure after treatment of an early lesion is hard to sell. To minimise the risk of such catastrophes, accurate staging is of utmost importance in order to avoid local procedures for advanced lesions.[61-63]

Improving survival

As mentioned earlier, pre-operative radiotherapy decreases local recurrence risk but has no survival benefit in TME treated patients. Local recurrence is thought to affect survival, but apparently, an absolute difference of "only 5.3%" is too small to impact on survival. Moreover, distant failure is accountable for mortality and is substantial regardless radiotherapy (25.8% vs. 28.3%, P=0.387). So far it is unknown whether adjuvant chemotherapy which is standard in colon cancer patients with nodal involvement, may improve survival in rectal cancer patients that have been treated with 5x5 Gy and TME. In the past adjuvant treatment has proven to be ineffective for rectal cancer patients.[64] This was however in the era of conventional surgery when local recurrence risk was major. Now that local failure is no longer a confounding factor due to the beneficial effects of both TME and radiotherapy, the matter needs to be addressed again. The SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus Tme) Trial randomises stage II/III rectal cancer patients that have had 5x5 Gy plus TME between oral capecitabine and observation. Unfortunately, trial accrual is slow leaving this important question unanswered. In the mean time more effective chemotherapeutics have been introduced in the field of colon cancer[65,66], opening possibilities for new clinical trials. An important difference with previous trials in the past decades is that pre-operative work up has become more accurate. Digital examination has been replaced by endoultrasound and MRI in many centers, leading to distinction between lesions that may be removed by either local excision, laparotomy or only after short term or prolonged neoadjuvant treatment. This development calls for inventive trial designs with adequate power to answer multiple questions.

Minimising the risk of symptomatic anastomotic leakage

Multimodality treatment of rectal cancer aims for adequate local control and prolonged survival. Apart from side late side effects on bowel, sexual and bladder function, acute morbidity

is important as well. In chapter 2 the acute side effects of radiotherapy using a 2 portal technique are extensively described. In the mean time, technique has changed substantially and Marijnen et al.[67] concluded, after describing the acute side effects of 5x5 Gy in the TME trial that "preoperative hypofractionated radiotherapy is a safe procedure in patients treated with TME surgery, despite a slight increase in complications when compared with TME surgery only." Indeed, apart from perineal wound dehiscence in APR patients, there are no significant clinical acute side effects that can be ascribed to radiotherapy. Apart from postoperative death, the most important complication after rectal surgery is anastomotic failure. There was no significant difference between irradiated and non-irradiated patients (10.9% versus 12.3%, P = 0.517).[68] Nevertheless, the rate of leakage is substantial, calling for further action. According to the multivariate analysis of the TME trial, both the construction of a temporary stoma and the placement of a drain in the presacral space are the only two factors correlated with a lower risk for leakage. It is noteworthy that there is no unanimous policy considering these two issues among surgeons in the Netherlands. Therefore, a national working party has been installed in order to reduce the morbidity and mortality associated with symptomatic leakage throughout the Netherlands. Guidelines will be evidence-based. Important questions that need to be asked for the individual rectal cancer patient are: what is the estimated risk for leakage prior to surgery (location of the tumour, gender, nutritional state etc.)? Is it possible to decide prior to surgery and not during surgery whether a stoma needs to be constructed (bowel function prior to multimodality treatment, likelihood of stoma reversal in a second procedure etc.)?

Laparoscopic resection of rectal cancer

Without elaborating on this hot topic, few words must be side on laparoscopy as surgical treatment of colorectal disease. For both benign and malignant diseases of the colon, laparoscopy is increasingly performed. The reported advantages are earlier recovery of bowel function and shorter hospital stay, improved quality of life without compromising oncological outcome.[69,70] Even despite perioperative optimization of open surgery using enhanced recovery programs, length of hospital stay is lower following laparoscopic surgery.[71] Moreover, the costs of the laparoscopic approach are only marginally higher than of open surgery.[72] Schwenk et al.[73] recently stated in a Cochrane systematic review including 25 randomised controlled trials that laparoscopic colonic resection "shows clinically relevant advantages in *selected* patients". Indeed, it is likely to assume that laparoscopy, especially in the early phase of the individual surgeon's learning curve, is only proposed to patients who are not likely to suffer from major postoperative complications. Moreover, many reports are from single-center institutions that have been able to gain a wide experience in laparoscopic colon resections. Finally, not only length of hospital stay should be of interest. The local infrastructure for postoperative care after hospital discharge should be accounted for as well: is the patient staying at home

without any (para)medical help or is he staying at "recovery hotels" hiring qualified nurses, therapists and home aides to meet all the patient's needs?

Rectal cancer seems a different entity. Considering its location in the lesser pelvis, it's a technically more demanding procedure requiring a long learning curve. Reports on laparoscopy are almost exclusively from non-randomised studies executed in experienced centers. Nevertheless, short term outcome may not always be as favourable (anastomotic leakage up to 17%)[74], and functional outcome may be unsatisfactory.[75] Laparoscopy is said not entail any oncological disadvantages.[74] However, focussing on the technical aspects of laparoscopy should not obscure the need for detailed preoperative work up, leading to unacceptable rates of palliative resection up to 25%[76], increased rates of positive resection margins[77] and local recurrence rates of 21%[78], putting us back in time when blunt dissection of rectal cancer was the norm. In conclusion, prior to introduction of laparoscopy for rectal cancer on a large scale, randomised controlled trials need to be awaited (COLOR II amongst others), surgeons need extensive training, and preoperative work-up should be standardized.

QUALITY ASSURANCE

Everyone involved in the treatment of cancer aims for improved treatment outcome. A tool to accomplish this goal is to increase the quality of the services that are delivered to cancer patients. For both gastric and rectal cancer, quality is increased by achieving good locoregional control. Achieving adequate local control is a matter of team work: radiologists play a profound role in preoperative imaging of rectal cancer, radiation and medical oncologists decrease tumor burden in case of locally advanced disease by administering prolonged chemoradiation, increasing the likelihood that the surgeon can perform a curative resection.

For gastric cancer, there are wide variations in outcome, calling for intervention. One possible way to improve quality, is to increase case volume, especially as surgery is the cornerstone of the treatment of gastric cancer. The literature on the relationship between volume and outcome is extensive and beyond the scope of this concluding chapter. It was Luft[79] who first explored the relationship in 1979 and concluded that there was a strong inverse relationship between hospital volume and mortality. Not many years ago, Birkmeyer[80] et al. investigated cardiovascular procedures and major cancer surgery and concluded accordingly. The mechanism of this persistent relationship is not completely understood. Possible confounding factors are the availability of well equipped staff and medical services, high quality of postoperative (intensive) care, and last but not least training of medical staff. Considering the latter, well-trained expert surgeons tend to work more often in high-volume hospitals, being prepared to focus on a relatively small area of surgical practise, troubling the volume-outcome relationship. Now that surgery for benign gastric diseases has become

a rarity and the incidence of gastric cancer is dropping, it is difficult to gain a certain level of expertise in gastric cancer treatment All together, for gastric cancer, concentrating cases in expert institutions seems the most logic means to improve nationwide outcome. Before appointing these expert centers, insight must be gained in the results of each treating center. In the United States the National Cancer Data Base (NCDB) collects detailed information on demographic and tumour statistics as well as treatment outcome for each cancer case in the US. Each year, every participating hospital receives a detailed and confidential report indicating how "good or bad" the center performs in comparison to regional and national benchmarks. This national non-governmental initiative has been a resource of cancer epidemiology throughout the years[81,82] and serves as a huge source of information for the benefit of quality assurance initiatives. Noteworthy is the low budget of 1-2 million dollars for maintaining this nationwide database.

In parallel, in Sweden, the Swedish Cancer Register has been introduced, making it mandatory by law(!) for each surgeon and pathologist to report each new cancer case including the surgeon and assistant surgeon who are involved in the treatment as well as information on surgical treatment (i.e. type of resection, curative intent, general and surgery-related postoperative complications etc.) Moreover, follow-up must be reported each year. Each year feedback on treatment outcome is given to all units. The Rectal Cancer Registry in Sweden has run for 9 years now and has included over 13.000 patients, from each center at least hundreds of patients. Now it has become possible to draw conclusions for each center, based on median results of specific endpoints. When centers do not reach standards, set by the surgical community, they may consider stop treating rectal cancer patients or seek additional training. Working in this way, treatment outcome improves. Although it is encouraging to see that trial results are superior to historical controls[83], it is important to realise that the majority of cancer patients is treated outside the framework of clinical trials. These patients also need to benefit from ongoing developments as well.[84,85] Finally, extensive training by experts is a prerequisite of improving treatment outcome: the acknowledgement that local recurrence of rectal cancer was a major problem in Sweden urged the medical community to acquire the TME technique by building up a training program and hiring Mr Heald, pioneer in TME surgery who teached this new surgical technique throughout Sweden. Similar initiatives were undertaken successfully in the Netherlands and Norway.[86,87] Yet, there is major room for further improvement, illustrated by the aforementioned challenges in rectal cancer treatment. In an attempt to meet challenges, a multidisplinary approach is necessary as is being employed currently in the Pelican Center Foundation, Basingstoke UK[88,89], offering training courses on colorectal malignancies applying MRI scanning in the preoperative work-up. Also, from economic point of view, it makes common sense to invest more in multidisciplinary training: Phil Quirke[90] calculated that the costs of multidisciplinary training in rectal cancer treatment amount only £200 per patient. Evidence shows a 20% reduction in cancer deaths through extensive training, making the total costs of each life saved £1000. For comparison,

by the introduction of novel chemotherapeutics as irinotecan and oxaliplatin the median survival of patients with metastastic colorectal cancer has improved over the past decade from 12 months (fluorouracil) up to 21 months.[91] Although these advances are commendable, the costs of the initial 8 weeks of treatment have increased 340(!)-fold from US$ 63 to US$ 21.033.[92]

In order to employ our resources in our struggle against cancer effectively, national cancer plans are crucial. Urged by the long waiting lists and worst treatment records in Europe, the United Kingdom launched the NHS Cancer Plan in 2000. Australia, Canada and New Zealand also have plans in place. France acknowledged the need for a comparable plan in 2003 and set up the National Cancer Institute (known as the INCa) employing 185 staff members within 6 months. The INCa initiated a cancer plan with a total of 70 key areas, all being precisely funded and evaluated. An expert committee lead by David Kayat, a medical oncologist and leading figure in France, calculated how much execution of the plan would cost. They asked the government for 1.7 billion euros, and they received the grant. It is a major plan including various measures: centralisation of basic research into 7 large regional research centers and structural coordination of cancer care. There is also room for raising the price of tobacco and buying the tobacco industry off, as well as for funding of television campaigns on the dangers of sun exposure. In 2004, a national plan against cancer was formulated in the Netherlands focusing on prevention, screening and treatment. Although the initiative is laudable, no concrete measures are taken considering organisation, funding and implementation. Putting pens to paper is not enough, long term vision and adequate funding is the key.

In conclusion, now that cancer mortality will overtake death from cardiovascular disease within a couple of years (http://www.kwfkankerbestrijding.nl/), it is time to decide how we will strike back as effectively as possible. When treating solid malignancies, setting up multidisciplinary teams involving organ-related specialists seems the key, with an emphasis on surgical training in technically demanding procedures as gastric and rectal cancer surgery. Within the EORTC, unfortunately there are no longer funds available for surgical quality assurance. The importance is however acknowledged: the European Journal of Surgical Oncology devoted a complete issue in august 2005 to the benefits of surgical QA. Recently, the European Society of Surgical Oncology released additional funds for surgical fellows, backing up this important area of surgical research. If governments are seriously willing to meet the challenge of combating cancer, investing in meaningful cancer plans and multidisciplinary training seems the only way.

SUMMARY

Cancer is a world wide health problem. Each year 10.9 million people are diagnosed with cancer. It is estimated that worldwide 24.6 million people are alive who have received a diagnosis of cancer in the last five years. In Western countries cancer incidence is increasing rapidly. In 2002, there was a cancer incidence in Europe of 873,700 cases, in Northern America of 1,570,500 patients (http://info.cancerresearchuk.org/cancerstats/). Of all malignancies solid tumours constitute the vast majority. Bowel, breast, lung and prostate cancer account for nearly half of all new cases.

Improving the quality of care aims at improving locoregional control, and thus survival. Numerous initiatives have been successfully employed in order to improve quality of radiotherapy and medical oncology. Although surgery is generally acknowledged as the mainstay of the treatment of solid tumours, surgical research encounters important difficulties: pharmaceutical companies do not release substantial funds to promote surgical research, neither seem governmental institutions willing to support trials investigating differences in surgical techniques. This possibly relates to the fact that every operation is considered a unique event which may hinder standardisation, a vital part of research when testing new treatment regimens. There is however a need for standardisation and uniforming surgical treatment: by controlling surgery, heterogeneity in patient outcome, caused by variation in surgical treatment, is removed as much possible. There are not many clinical trials that have made serious efforts to standardize surgery in order to reduce its confounding influence of surgery on treatment outcome. The Dutch D1D2 Gastric Cancer Trial[4,93] and the TME trial[94], both prospective randomised trials, have done their utmost to instruct surgeons onsite, to teach and control surgical treatment and to record every vital treatment detail.[95,96] The D1D2 trial investigated the role of extended lymph node dissection (D2) compared to limited lymph node dissection (D1) in patients with gastric cancer. The Dutch TME trial tested short term preoperative radiotherapy in rectal cancer patients who were treated with TME (Total Mesorectal Excision). The current thesis focuses on both trials.

Chapter 1 serves as a general introduction, describing the background and the outline of this thesis.

Chapter 2 is a review of the various aspects of gastric and rectal cancer treatment. Although the need for standardised and quality-controlled surgery is emphasized, the value of adjunctive treatment regimens is discussed as well.

Chapter 3 is an editorial that was released in the Journal of Clinical Oncology, reflecting upon a Japanese study (published in that same issue) that investigated the value of adjuvant chemotherapy in gastric cancer patients. 252 serosa negative gastric cancer patients were

randomised in a phase III trial between intravenous mitomycin, fluorouracil and cytarabine, twice weekly for the first 3 weeks after surgery followed by oral FU for the next 18 months (arm 1) versus surgery alone (arm 2). The primary end point was relapse-free survival. According to Japanese practise, 98% underwent extended lymphadenectomy (D2 dissection) and relapse-free survival was impressive: 88.8% resp. 83.7%. Remarkably, only 2 patients (none in the combination-treatment group, 2 in the surgery alone group) developed a local recurrence. These favourable results are beyond any expectation when treating Western gastric cancer patients. The editorial deals with differences in disease stage, surgical technique and type of chemotherapy that may explain these gross differences between Japan and Western countries.

In *chapter 4* the value of the "Maruyma Index of Unresected Disease" is studied. It was concluded in both the British MRC trial as well as the Dutch Gastric Cancer Trial (both large prospective randomised phase III trials) that there was no benefit from extended lymph node (D2) dissection in gastric cancer patients. However, postoperative mortality was substantial in the D2 arms of both trials, which possibly obscured a survival benefit of extended lymph node dissection. There are several ways to reduce the risk of postoperative mortality: according to subgroup analyses of the Dutch Gastric Cancer Trial, patients older than 70 years have substantial risk for postoperative mortality, making them less suitable candidates for extended surgery. Also, the risk of postoperative complications is reduces when spleen and pancreatic tail are preserved. Meanwhile, organ preservation techniques have been introduced successfully.Moreover, resection of these organs is no longer considered necessary for adequate nodal clearance. Finally, prevention of unnecessary resection of tumour negative nodes minimises the risk of postoperative complications as well. The question is however, how nodal clearance can be limited without compromising both staging and survival. The Maruyama program offers a possible solution. The program requires entry of 7 patients and tumour characteristics of an individual patient and then simply matches this case with very similar cases previously treated at the National Cancer Center Hospital in Tokyo, Japan. In this manner the computer gives a prediction of the likelihood of nodal involvement of each of the 16 lymph nodes stations. The Maruyama Index of Unresected Disease (MI) was defined as the sum of regional nodal disease percentages for stations that were not removed by the surgeon. The MI was introduced for the first time by the investigators of the SWOG trial that showed that postoperative chemoradiation was beneficial in gastric cancer patients. The MI turned to be a prognostic factor and stressed that there was substantial undertreatment in this US trial. Chapter 4 describes the value of the MI in 648 patients of the Dutch Gastric Cancer Trail who underwent a curative resection. According to the multivariate regression analysis, MI turned out to be a significant independent predictor of overall survival and disease-free interval. (HR 1.45, P = 0.016 resp. HR 1.72,, P = 0.010). The MI enables the surgeons to match the extent of surgical resection with the extent of regional disease. Obtaining a low MI seems

preferable in stead of dissecting the complete N2 echelon, exposing patients to substantial risks of postoperative death. The next step is prospective testing of the value of the MI.

Chapter 5 has tested a model that serves as a predictor of survival after gastric cancer treatment. Apart from treatment (surgery and its extent, adjuvant (chemo)radiotherapy etc.), there are other factors such as age, sex, the stage of disease at presentation and tumour location and morphology that determine a patient's prognosis. Current staging modalities focus solely on tumour depth (T stage) and the presence of nodal involvement (N stage). Nomograms are models that integrate other prognostic factors as well. One could argue that the need for adequate prognosis clinically irrelevant, as there is no role (yet) for adjuvant treatment in the Netherlands. However, both patients and doctors have a growing interest for individual-based specific information on survival prognosis. The nomogram sees to this need. The nomogram that was developed for gastric cancer was tested in only one high-volume US center (Memorial Sloan Kettering Cancer Center, NY, USA). We attempted to validate the nomogram in patients included in the Dutch Gastric Cancer Trial. Also, the discriminating value of the nomogram was studies in relation to the AJCC staging system.

There were 459 eligible patients with available information for the nomogram calculation. Nomogram discrimination was superior to that of AJCC stage grouping (concordance index 0.77 vs. 0.75, $P < 0.001$, Z-test) and proved to be an accurate predictor of 5- and 9 year disease-specific survival. Moreover, patients within different AJCC stages with heterogeneous prognosis were successfully discerned, using the nomogram. In comparison, the AJCC staging system that is presently used is unable to identify subsets of patients with homogeneous prognoses. By classifying patients according to differences in prognosis, suitable candidates for novel adjuvant treatment regimens may be identified. The nomogram is freely available in software from www.nomograms.org.

Chapter 6 describes a study that investigated risk factors for symptomatic anastomotic leakage after TME for rectal cancer. The benefits of TME are beyond any dispute: both local control and survival are superior compared to historical controls, and functional outcome (bladder and sexual function) has improved substantially through working under close vision of important nerve structures. Anastomotic failure remains however a significant problem. As anastomotic failure causes substantial morbidity and even mortality, all efforts should be directed towards the reduction of risk of anastomotic dehiscence.

Nine hundred twenty-four patients undergoing low anterior resection with primary anatomises were included in this study. Of all possible risk factors known from the literature, the presence of a diverting stoma (8.2% vs. 16.0%, RR 1.89 (1.24-2.90), P=0.003) as well as the placement of a drain in the pelvic area (9.6% vs. 23.5%, RR 2.53 (1.57-4.09, P<0.001) were correlated with a decreased risk of anastomotic failure. Interestingly, there were wide variations

in the policy regarding stoma construction and pelvic drainage, emphasizing the need for standardisation in order to avoid this major complication after TME.

Chapter 7 reports on the late side effects of both TME and short term radiotherapy. In the past, preoperative short term radiotherapy followed by conventional blunt dissection of the rectal tumour has been held responsible for increased bowel frequency, incontinence, urgency and emptying difficulties. We examined the late side effects in patients included in the TME trial. A questionnaire was sent to 708 patients who were alive and had no evidence of recurrent disease. 597 patients (87%) returned the questionnaire; the median follow up of responding patients was more than 5 years.

There was no difference between irradiated and non-irradiated patients regarding urinary function, stoma function and hospital treatment. However, irradiated patients reported increased rates of fecal incontinence (62% vs. 38%, P < 0.001), pad wearing due to incontinence (56% vs. 33%, P < 0.001), anal blood loss (11% vs. 3%, P = 0.004) and mucus loss (27% vs. 15%, P = 0.005). These data urge doctors to inform their rectal cancer patients reliably about the side effects of both radiotherapy and. Compared to radiotherapy, TME surgery is the main contributor to late bowel dysfunction. However, surgery is the only option that can lead to cure in contrast to radiotherapy that has merely benefits in terms of increased local control. The substantial additional long term side effect of radiotherapy on bowel dysfunction urges to tailor radiotherapy to those patients only who are most likely to benefit from it. However, pretreatment staging modalities presently used are not capable enough to accurately identify patients at risk for local failure.

Chapter 8 reports on the results of the TME trial after a median follow-up of 6 years. Early results after a median follow-up of 2 years showed a decrease in local recurrence risk (2.4 vs. 8.2%, P<0.001) in irradiated patients without any survival benefit (82.0% vs. 81.8%, P=0.84). It was hypothesized that there was no survival benefit yet due to a short period of follow-up.

There was a persistent significance in local recurrence risk at 5 years to the benefit of irradiated patients (5.6% vs. 10.9%, P < 0.001), yet there was still no survival benefit (64.2% vs. 63.5%, P = 0.902). Local failure is presumed to be a cause of death. However, an absolute difference of "only" 5.3% is perhaps too small to affect survival significantly. Moreover, distant failure occurs often regardless the administration of radiotherapy (25.8% vs. 28.3%, P = 0·387) and is an important cause of death.

In order to minimise the late side effects as described in chapter 7, subgroup analyses may be valuable. According to these analyses only tumours between 5 and 10 centimeters from the anal verge benefit from radiotherapy (3.7% vs. 13.7%, P<0.001). Local failure is uncommon in proximal lesions and the effect of radiotherapy is not significant (3.7% vs. 6.2%, P=0.122), making the "numbers needed to treat" in order to prevent one local recurrence substantial. For distal lesions there is neither any significant effect of radiotherapy (10.7% vs.

12.0%, P=0.578). An important confounding factor in distal rectal cancer is the considerable rate of circumferential resection margins. When tailoring the indications for radiotherapy by performing subgroup analyses on tumor height, it must be stressed that exact determination of tumour location, and thus the a priori chance of local failure is difficult.

The effect of radiotherapy depends also the stage of disease. According to subgroup analyses, only pTNM stage III rectal cancer (nodal involvement) benefit from radiotherapy. Apparently, with the involved nodes having removed, preoperative radiotherapy is able to treat (microscopic) nodal disease beyond the plane of surgical resection. Unfortunately, there are presently no reliable means that can be used in the preoperative work up that can identify patients with nodal involvement.

Short term preoperative radiotherapy achieves a relative risk reduction of 49% in local recurrence risk. Although there is no detectable survival benefit, this radiotherapy regimen remains a valuable treatment modality as the severe symptoms associated with local failure are prevented in many rectal cancer patients.

Chapter 9 reports on a benchmark study that was performed in order to evaluate multimodality treatment of locally advanced rectal cancer. The Catharina Hospital in Eindhoven, the Netherlands, is a national referral centre for rectal cancer patients in whom a radical resection is not likely to be obtained. All consecutive patients with a rectal tumour infiltrating into or less than 2 mm distance to the mesorectal fascia on MRI were included (n=252). For these lesions multimodality treatment is given involving prolonged radiotherapy of 50,4 Gy (1,8 Gy per fraction) and intra-operative radiotherapy (10-15 Gy) at the area of risk. Also, chemotherapy was administered (5FU and leucovorin, later replaced by oral capecitabine and oxaliplatin). Results of this multimodality treatment were compared to data from TME trial: patients with operable, mobile pT3/4 disease without distant failure at time of operation were used as a benchmark.

Three year local recurrence rate was significantly lower in TME trial patients: 5% and 17% (P = 0.0001). Interestingly, in as much as 83% of the patients wit locally advanced cancer a negative circumferential resection margin could be realised, compared to 75% of the TME trial patients (P = 0.037). Overall survival after 3 years was similar (76% for TME trial patients and 67% in case of locally advanced lesions, P = 0.071). Both circumferential margin status as lymph node status were important outcome parameters in both groups, for overall survival, metastases free survival and local recurrence. When chemoradiation is not able to achieve sufficient tumour down sizing and –staging, resulting in positive resection margins, the prognosis of patients of locally advanced lesions is considerably worse than of patients with operable disease with positive margins.

Chapter 10 is a review dealing with the role of sentinel node biopsy (SNB) in breast, gastric and colorectal cancer. SNB has been introduced to reduce the extent of axillary lymph

node dissection and thus the associated postoperative morbidity without compromising adequate staging, locoregional control and survival (breast cancer). Another advantage is the possibility to search the sentinel node for the presence of minimal residual disease (MRD) that might have prognostic influence. The review addresses the variation in technical aspects and outcome of SNB and MRD assessment. Considering the substantial variation in reported techniques there is a need for quality control leading to standardization of SNB and pathological examination to enable reliable comparison of studies. Only then a consensus regarding diagnostic and therapeutic strategies may arise.

Chapter 11 is a general discussion on future directions of gastric and rectal cancer treatment. Also a summary of the thesis is given.

Chapter 12 provides a summary in Dutch. Also, all centers that participated in the Dutch Gastric Cancer Trial and the TME trial are acknowledged.

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