Quality assurance in surgical oncology

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Quality assurance of surgery in gastric and rectal cancer

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Abstract

Multimodality and quality controlled treatment result in improved treatment outcome in patients with solid tumours. Quality assurance focuses on identifying and reducing variations in treatment strategy. Treatment outcome is subsequently improved through the introduction of programs that reduce treatment variations to an acceptable level and implement standardised treatment. In chemotherapy and radiotherapy, such programmes have been introduced successfully. In surgery however, there has been little attention for quality assurance so far.

Surgery is the mainstay in the treatment of patients with gastric and rectal cancer. In gastric cancer, the extent of surgery is continuously being debated. In Japan, extended lymph node dissection is favoured whereas in the West this type of surgery is not routinely performed with two large European trials concluding that there is no survival benefit from regional lymph node clearance. Postoperative chemoradiation is part of the standard treatment in the United States, although its role in combination with adequate surgery has not been established yet. These global differences in treatment policy clearly relate to the extent and quality of surgical treatment.

As for gastric cancer, surgical treatment of rectal cancer patients determines patient's prognosis to a large extent. With the introduction of total mesorectal excision, local control and survival have improved substantially. Most rectal cancer patients receive adjuvant treatment, either pre- or postoperatively. The efficacy of many adjuvant treatment regimens has been investigated in combination with conventional suboptimal surgery. Traditional indications of adjuvant treatment might have to be re-examined, considering the substantial changes in surgical practise.

Quality assurance programs enable the introduction of standardised and quality controlled surgery. Promising adjuvant regimens should be investigated in combination with optimal surgery.

Keywords: gastric cancer, rectal cancer, surgery, quality assurance

1 INTRODUCTION

In recent years, quality of care is increasingly acknowledged as a crucial factor in the treatment of cancer patients[1]. Keys to improved treatment outcome are multidisciplinary treatment and standardised, quality controlled therapy. These are, at least for a substantial part, integrated into most of the clinical trials. This may partly explain why trial patients often experience a survival advantage over non-participating patients[2]. The goal of (randomised) clinical trials is primarily to prove the advantage of one treatment over the other. Ultimate goal of all research efforts should be however, to improve cancer care for all cancer patients and to expand the knowledge obtained from clinical research to a broader patient population. This means that the level of quality control carried out in a trial, should ideally be maintained in daily clinical practise and integrated into oncological care in a standardised manner. Quality assurance is an area of research that is engaged in evaluating and interpreting variations in treatment and linking them with treatment outcome. To improve outcome, quality assurance focuses on the complete set of systematic actions that is required to achieve a certain standard of care, that is considered possible and feasible to achieve and to maintain. This implies that there is need to formulate a minimum standard of care, to define an acceptable level of variation in treatment outcome, and consequently, to identify factors that are crucial to achieve this standard. Considering the ongoing advances in oncological care, especially in the surgical area, it is key to appreciate these advances for cancer patients and to make every effort to put them into practise.

Although quality assurance is still in childhood, several quality assurance programmes have been employed successfully in chemotherapy[3-6] and radiotherapy[7-14]. In surgery however, that is generally considered the cornerstone of treatment of patients with solid tumours, there has been remarkable little attention for quality control and standardization so far. Of course, surgery is often still looked upon as merely a craft, which may hinder standardization: quantifiable parameters are assumed hard to define and to measure, and each surgical performance is considered a unique event with irreproducible and unpredictable events. However, recent large scale surgical initiatives have undoubtly shown that surgeons are willing to reflect upon their performance and are eager to improve their surgical technique[15-17]. These initiatives showed clearly that training and audit of surgeons is feasible and can result in significant improved local control and survival when compared to historical controls[18]. Through surgical training programmes it has become clear that many treatment failures, that had often been considered to be a result of aggressive biological tumour behaviour, are in fact caused by inadequate local therapy[19]. The changes in surgical practise have to be taken stock of by not only surgeons, but also by radiation and medical oncologists. With the advent of superior surgical techniques, one may have to re-examine the role of (neo-)adjuvant treatment regimens that often have been established in the era of suboptimal surgery. This review deals with the recent developments in the treatment of gastric and rectal

cancer with an emphasis on quality control. Gastric and rectal cancer will be discussed here as surgical treatment of these malignancies is subjected to ongoing debate and has changed substantially in recent decades respectively.

2 GASTRIC CANCER

2.1 Introduction

Although its incidence is declining in Western Europe[20], gastric cancer remains the second most common cause of cancer death worldwide[21]. The decreasing mortality in the West due to gastric cancer is almost solely related to a decreased incidence. This is in contrast to Japan, where apart from the decreasing incidence, overall cure rates are a contributing factor as well. Fuchs and Mayer[22] compared in 1995 stage specific survival between the United States and Japan and noticed remarkable differences in both stage of disease and stage specific 5 year survival rates in favour of Japan. There is some evidence that differences in biological behaviour are responsible for these differences: Japanese patients are younger at the time of diagnosis, have less often proximal lesions, and more often gastric cancer of the "intestinal" type whereas in the West, the diffuse type is more often seen[23]. Bonenkamp et al.[24] compared patient characteristics from Dutch, Japanese en German centers: Japanese patients were on average 3 years younger than German and 8 years younger than Dutch patients, while they had more T4 tumours. Five year survival rates were superior for Japanese patients without an difference in sex distribution, histology and lymph node involvement. In another report from Bollschweiler et al.[25], two patient populations from Germany and Japan were compared. Univariate analysis of 5 year survival rates were 44% and 77% respectively. However, German patients had fewer T1 stage, fewer N0 stage and more M1 stage tumours. Also, they were on average 6 years older and had twice as many proximal tumours. Finally, mass screening as employed in Japan, provides an opportunity to detect gastric cancer in an early stage, and is associated with improved survival rates compared to patients who are not subjected to screening examination[26]. Although the biological differences may at least partly explain the differences in outcome between Japan and the West, the global discussion focuses predominantly on the extent of surgery.

2.2 Surgery

Surgery is the only possible treatment that can lead to cure. On January 22nd 1881, Theodor Billroth was the first to perform a successful operation on a gastric cancer patient, a subtotal gastric resection with a gastro-duodenal anastomosis. The 43 years old woman had a favourable postoperative course, was discharged 26 days after surgery, but died of recurrence 14 months later[27]. For Billroth, the operation was a triumph, and 14 years later, his series comprised 257 cases. Since then, surgical techniques have evolved and improved substantially

with lower rates of postoperative morbidity and mortality and better survival. When looking at a review of articles published in English since 1970, it becomes clear that in recent decades, the number of patients that underwent surgery increased as well as rates of complete resection. These figures are accompanied by mean 5 year survival rates ranging from 21% before the 1970s to 55% in the 1980s[28]. Despite this progress in gastric cancer treatments the global debate on the most appropriate surgical technique is still heated[29].

2.2.1. Extent of gastrectomy

In earlier years, the extent of gastrectomy was still a matter of controversy, especially for cancer in the distal/middle stomach. An *en principle* total gastrectomy, i.e. a total gastrectomy, even when adequate clearance of margins can be obtained by subtotal resection was initially promoted in the United States[30] and France[31] as the preferred surgical treatment. However, several non-randomised series showed that total and subtotal gastrectomy resulted in comparable oncological outcome[32-34]. Moreover, in a Norwegian study, there was a significant lower morbidity rate for subtotal resections in comparison to total gastrectomy(28% versus 38%)[35], which was in line with results from a German study (23% versus 48%)[36]. Also, two convincing prospective randomised trials showed no significant differences 5 year survival rates between subtotal and total gastrectomy[37,38]. The more conservative operation is to be favoured in patients with cancer of the lower or middle stomach, as total gastrectomy is often accompanied by splenectomy which has an adverse effect on postoperative complications and the susceptibility to infections[39-42]. So, one could argue that the extent of gastrectomy is no longer a controversial issue: subtotal gastrectomy is the treatment of choice unless the tumour is localised proximally in the stomach, there is a diffuse tumour growth pattern or a safe proximal margin cannot be obtained. The importance of complete tumour removal was investigated by Songun et al.[43] who showed that margin involvement, which was seen in 5.9% of the evaluable patients in the Dutch Gastric Cancer Trial, was associated with significantly worse survival. It was concluded from this study that frozen section examination should be routinely performed, especially in patients with poorly differentiated, signet ring cell or anaplastic tumours.

2.2.2. Extent of lymph node dissection

Unlike the extent of gastrectomy, the extent of lymph node dissection remains among surgeons subject to heated debate. It was as early as 1889 that Mikulicz propagated lymph node dissection in addition to gastrectomy with removal of the pancreatic tail if necessary[44]. Cunéo showed in 1900 that locoregional lymph nodes played an important role in the metastasis of gastric cancer[45]. Gastric cancer is a disease in which local regional control is difficult to obtain[46]. In order prevent failure and to improve survival, all efforts should be directed toward adequate local therapy. The main discussion centres on the question; what is

adequate local therapy? Is this the territory of the surgeon alone or may have (neo-)adjuvant treatment any value as well?

As mentioned before, reported survival rates have always been consistently better in Japan than in the West. Extended and standardised lymph node dissection as employed in Japan, is according to the Japanese investigators the main explanation for their superior treatment outcome. In the East, it is believed that lymph nodes are *governors* of metastatic disease. According to this philosophy, it is considered crucial to remove these lymph nodes to prevent metastasis and to improve survival. This extended (prophylactic) lymph node dissection is associated with accurate staging, as understaging due to failure to detect tumour involvement of undissected lymph nodes is very unlikely. This approach is contrast to Western believe that states that lymph nodes are merely *indicators* of disease: lymphadenectomy is solely performed in order to stage patients and subsequently to plan adjuvant treatment and not necessary to cure them. Lymph node involvement in gastric cancer is thus thought to be a sign of widespread disease and poor prognosis. These two opposite movements determine the extent of lymph node dissection.

The Japanese Research Society for the Study of Gastric Cancer (JRSGC) has provided strict guidelines for standardization of surgical treatment and pathological examination[47]. According to these guidelines, 16 different lymph node compartments are identified around the stomach (figure 1). Basically, along the lesser curvature stations 1, 3 and 5 are discerned and along the greater curvature stations 2, 4 and 6. these perigastric nodes are grouped N1, whereas nodes along the left gastric (7), common hepatic (8), celiac (9) and splenic (10,11) arteries are grouped N2. Further lymph nodes of stations 13 to 16 have been described. A D1 lymph node dissection entails removal of the greater and lesser omentum and all its perigastric nodes. The extended D2 dissection involves dissecting not only the perigastric nodes, but also the regional N2 nodes. Convinced of the benefits of extended lymph node dissection, Japanese investigators have always been reluctant to perform a randomised trial comparing limited and extended lymph node dissection. In Japan, it is generally considered unethical towards patients and deemed unfeasible among surgeons to run a such trial. Considering the superior outcome in Japan, attempts have been made to introduce extended surgery into the West. Four randomised trials tested D2 against D1 dissection.

Dent et al[48]. were the first to perform a prospective randomised study of gastrectomy with or without D2 dissection. From 1982 to 1986 608 cases were evaluated, and 403 were deemed surgical candidates; as few as 43 patients turned out to be eligible for the trial. The age difference between the two patient populations was remarkable: D2 patients were older (55.8 vs. 45.1 years), and were more often male (15 male patients in the D2 group, 12 in the R1 group). No survival difference was noticed, but the number of patients was very low, which makes it very hard to detect differences that may be small, but clinically relevant to both patients and their doctors. Moreover, there was no explicit quality control and this was a

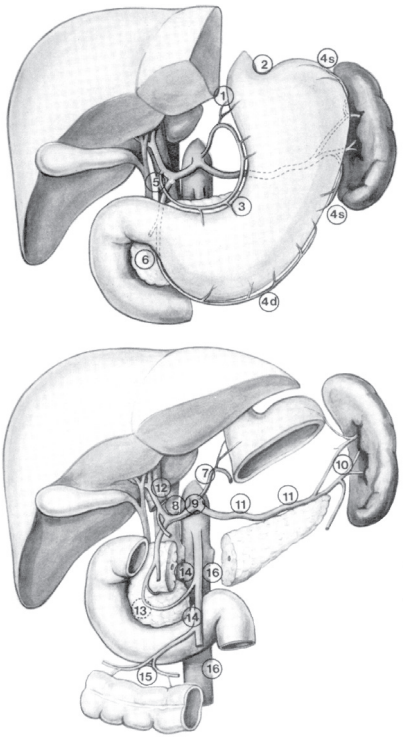

Figure 1. Lymph node stations surrounding the stomach. 1 = right cardial nodes; 2 = left cardial nodes; 3 = nodes along the lesser curvature; 4 = nodes along the greater curvature; 5 = suprapyloric nodes; 6 = infrapyloric nodes; 7 = nodes along the left gastric artery; 8 = nodes along the common hepatic artery; 9 = nodes around the coeliac axis; 10 = nodes at the splenic hilus; 11 = nodes along the splenic artery; 12 = nodes in the hepatodoudenal ligament; 13 = nodes at the posterior aspect of the pancreas head; 14 = nodes at the root of the mesenterium; 15 = nodes in the mesocolon of the tranverse colon.

single institution trial, conducted by only 3 surgeons. Finally, there was a very low eligibility rate, which makes the trial not representative for all patients with gastric cancer.

From 1987 to 1991, 55 patients with antral tumours in Hong Kong underwent subtotal gastrectomy and were randomised to either D1 or D3 dissection[49]. Only 3 surgeons accounted for 75% of the cases. Distal pancreatectomy and splenectomy were part of the D3 dissection. The two patient groups had similar baseline characteristics. Actually, the D1 group had better median survival (1511 vs. 922 days, $p < 0.05$) with a shorter operative time (140 vs. 160 minutes, $p < 0.05$), less blood transfusions ($p < 0.05$), and shorter hospital stay (8 vs. 16 days, $p < 0.05$). One patient died in the D1 group and none in the D3 group (n.s.). Postoperative complications rates (mainly subphrenic abscess and esophagojejunal anastomotic failure) were around 10% and did not differ between the two randomised arms.

From 1986 through 1995 the British Medical research Council set up a prospective randomised trial investigating the possible benefits from D2 dissection over D1 dissection. D1 dissection was defined as a dissection of lymph nodes that were located within 3 centimetres

of the tumour, according to the 1987 TNM classification. D2 dissection concerned dissection of the so called TNM N2 nodes (celiac, hepatodoudenal, retroduodenal, splenic and pancreatic nodes, *depending on the location of the tumour*) with removal of the nodes located at more than 3 centimetres of the tumour. Surgical quality was guaranteed through pre-trial education which consisted of an operative booklet and videotapes of the requested operating procedures. Using a staging laparotomy and intraoperative frozen sectioning, randomisation of ineligible patients (i.e. patients with advanced disease or margin involvement) was limited to only 3 out of 400 randomised cases. The pancreatic tail was removed almost exclusively in the D2 group, the spleen was taken away frequently in both groups, but more often in patients assigned to D2 dissection. With a median follow-up of 6.5 years, 5 year survival rates were 35% for the D1 group and 33% for the D2 group(n.s.)[50]. Splenectomy and resection of the pancreatic tail seriously impacted on survival and proved to be independent predictors of poor survival. Moreover, there was notably increased postoperative morbidity (28% for D1 and 46% for D2) and mortality (6.5% for D1 and 13% for D2) in patients that underwent extended lymph node dissection[51].

Finally, from 1989 to 1993, Dutch gastric cancer patients were randomised between D1 and "Japanese D2 lymphadenectomy". Before the start of the trial, surgeons from 80 centres and eight expert consulting surgeons were extensively instructed to perform surgery according to the protocol of the Japanese Research Society for the Study of Gastric Cancer (JRSGC)[52]. 1078 patients were randomised prior to surgery of whom 82 were excluded for unavailability of a consultant surgeon, poor physical condition or lack of histological confirmation of the diagnosis. Of the remaining 996 patients, 711 underwent the allocated treatment with curative intent. At a median follow-up of 72 months, 5 year survival was 45% for the D1 group and 47% for the D2 group[53]. Morbidity and mortality were 25% and 4% in the D1 group and 43% and 10% in the D2 group respectively[54]. In conclusion, the results of all mentioned randomised trials do not favour the routine use of extended lymph node dissection for gastric cancer, at least not in Western patients.

The matter is however a bit more complicated. The trials that were initiated in South Africa and Hongkong had very few patients randomised and have to be considered underpowered to detect a clinical relevant difference. The British and Dutch trials included a large number of patients and had a good trial design, yet did not detect any significant survival difference. There is however some criticism raised against the two European trials.

First, despite elaborate quality control in the Dutch trial, there were surgical protocol deviations that blurred the intended distinction between D1 and d2 dissection. If lymph node stations were removed that were not to be harvested, this was called "contamination", whereas "noncompliance" was defined as the absence of lymph nodes that had to be harvested according to the protocol. Contamination occurred in 6% of D1 cases and noncompliance in 51% of D2 patients[55]. It became clear that, although detailed treatment guidelines were available, variability among surgeons was considerable. The protocol deviations were detected during

the early phase of the trial, which prompted the investigators to take additional to ensure protocol adherence: expert consultants paid more attention to protocol compliance, lymph node retrieval from the resected specimen was standardised and consistently performed by a specially trained surgical coordinator, immediately after each operation. Notwithstanding these unique efforts, the initiators of the trial concluded themselves that contamination in D1 resections and noncompliance in D2 resections lead to a partial homogenisation of the groups, undermining the likelihood of detecting any potential therapeutic advantage to D2 dissection. The MRC trial did not report on similar problems, simply because they did not investigate the level of surgical non-compliance.

Another important confounding factor in the Dutch and the British trial was the high postoperative mortality caused by splenectomy and pancreatectomy. Both procedures were considered compulsory during the course of the trials to ensure adequate clearance of especially stations 10 and 11. There is ample evidence that pancreaticosplenectomy is associated with increased postoperative morbidity and mortality[56,57], with a significant adverse effect on survival as well[37]. In the Dutch trial, the spleen and pancreatic tail were removed in as many as 38% and 30% of the D2 patients and were responsible for postoperative complications. Preservation of the spleen is important considering the high rates of anastomotic failure in patients that underwent a subtotal D2 gastrectomy. A most likely explanation is that in a D2 dissection, the left gastric artery is divided at its origin, which leads to only a marginal blood supply of the remaining short gastric arteries to the rest of the stomach, thus complicating anastomotic healing. In the meanwhile, organ preservation techniques have become available and are employed successfully with adequate clearance of the regional N2 tier, not only in Japanese but also in Western patients. Dedicated centres in Western Europe have reported mortality rates of less than 5% for extended lympadenectomy with organ preservation[58-60]. In contrary to earlier belief, it has become clear that preservation of the spleen does not compromise survival due to inadequate lymph node removal: a randomised trial from Chile found no survival benefit from splenectomy whereas morbidity was again significantly increased[61]. Another trial in Japan, studying the same matter is on its way[62].

A third and final reason why D2 lymph node dissection did not prove to be superior might relate to the fact that the surgical case load was rather low in both large randomised trials. As many as eighty hospitals participated in the Dutch trial; therefore, a mean of only two patients in any one hospital underwent extended lymph-node dissection in any one year. For this reason, quality control was mandatory, but apparently could not prevent the high postoperative complication rates. Publications on the relation between volume and outcome are numerous, also in gastric cancer, but far from unanimous. A retrospective study by McCulloch[63] and the results of the German Gastric Cancer Study[36] showed clear differences in outcome based on surgical experience whereas no such pattern was discovered among surgeons participating in the Dutch trial[64,65]. Recent reports from experienced centres do suggest however, that outcome improves with higher case-load[66]. This might relate to

low complication rates due to organ preservation that has become part of the standardised D2 dissection in specialized centres. Other factors may include superior surgical skill itself, optimal perioperative care, patient selection bias, or a combination of either these. Fact is however, that surgical gastric cancer treatment is increasingly centralised.

One important issue has been underexposed so far. There is one possible explanation why patients that undergo extended lymph node removal perform better. D2 dissection generally yields more lymph nodes for pathological examination than D1 dissection. The more lymph nodes are examined, the more accurate the staging will be. A so called stage migration[67] may occur when as a result of extended lymph node dissection, a proportion of the patients is assigned to a more advanced stage than would otherwise be the case. Of course, the prognosis is the same in both cases. If this phenomenon takes place, overall results in each stage improve, and the proportion of patients staged as having advanced disease increases. This stage migration has been held responsible for survival differences between Japanese and Western patients. In the Dutch trial, the stage migration effect was estimated by comparing stage specific 5 year survival rates between D1 and D2 patients. Prognosis of TNM stage II patients was 38% for D1 and 43% for D2 patients, for stage IIIA patients these rates were 10% and 29% respectively[68]. Upstaging occurred in as many as 30% of the D2 patients[55]. To limit the blurring effect of stage migration when comparing D1 to D2 dissection, standardization of surgery and pathological examination, as both the surgeon and the pathologist influence the number of lymph nodes that are examined.

So, there is no definite answer as to whether the gastric cancer patient should be treated with extended lymph node dissection or not. Removal of regional lymph nodes that may carry (micro)metastases makes sense either to prevent local failure, and perhaps also to improve survival. In the West, the main drawback from extended surgery has been until recently, the high rates of postoperative complications due to organ removal and/or low case load. The future looks promising with results from experienced centres in the West that have shown low rates of in hospital morbidity and mortality in combination with organ preservation. From quality assurance point of view, interinstitution and intersurgeon variability should be tackled by centralised treatment and strict protocol guidelines with adequate audit to ensure protocol adherence. This includes certainly standardization of pathological examination. There are still some important questions to be answered: is retrieval and investigation of each of the separate 12 or 16 lymph node stations really necessary and feasible in the West? Or is retrieval of at least 15 lymph nodes according to the present TNM classification without any specification on its location sufficient to perform an adequate staging? These questions have to be answered not only for staging purposes, but also to assess the efficacy of adjuvant treatment.

2.3 Adjuvant treatment

Although it is beyond the scope of this review, few words must be said on the role of adjuvant treatment. The discussion centers around the question whether adjuvant therapy is capable of increasing local and distant control and thus improving survival in addition to adequate surgery. This question has remained unresolved so far. The use of chemotherapy in gastric cancer is based on experience in the use of a wide variety of combinations of this modality in therapy for palliative management[69-73]. The chemotherapy regimen FAMTX (high dose methotrexate, high-dose 5 FU, doxorubicine and leucovorin) has been tested in a randomised fashion against 5-FU, doxorubicin and mitomycin (FAM regimen), showing a superior response rate (41% versus 9%, $p < 0.0001$), survival (10.5 months vs. 7.2 months, $p = 0.004$) for patients receiving FAMTX[74]. In concordance with the results of this trial, this regimen was considered a standard therapy in the mid 1990s, at least for patients with advanced disease. A few years later Webb et al.[75] compared FAMT with epirubicin, cisplatin and 5 FU (ECF) in patients with oesofagogastric cancer. ECF proved to be superior with regard to overall response rate (45% vs. 21%, $p = 0.002$) and median survival (8.9 vs. 5.7 months, $p = 0.0009$).

Adjuvant cytotoxic chemotherapy alone has been tested widely during the past three decades, and proven to be of limited value according to an early meta-analysis of Hermans[76]. Recent meta-analyses however, including trials studying novel agents, showed however, a marginal but significant benefit of postoperative chemotherapy[77-79]. The combination of radiation therapy and a fluorinated pyrimidine as a radiation sensitizer may possibly eradicate small amounts of residual or recurrent disease, in both gastric[80] and oesofageal cancer[81]. The US Intergroup study tested whether the combination of 5 FU/LV plus radiation therapy had any value to patients with resected gastric cancer. The study included 556 eligible patients and showed a significant overall survival benefit after postoperative chemoradiation (36 versus 27 months median overall survival in the surgery alone-group, $p = 0.005$). Moreover, there was increased local control after combined treatment with a relapse free survival of 19 months in the surgery alone arm, compared to 30 months in the chemoradiation arm[82]. The results of trial have lead to standardisation of this regimen in the United States. It is remarkable that this decision is based on a study in which 54% of the patients did not have a complete clearance of even the perigastric nodes. Although comparison of patient populations of two separate trials must be made carefully, the differences in outcome with the Dutch trial are striking: 6 year survival rates of Dutch patients undergoing D2 dissection were 47% compared to a 3 year survival percentage of 50% in the superior arm of the US trial. It seems that chemoradiation is capable of at least partly compensating suboptimal surgery. Its role however, in combination with good surgery remains questionable. The American initiators of the trial claim that their patients had more advanced disease than the Dutch patients, which precludes any reliable comparison. Indeed, almost 70% of the US patients had at least a T3 lesion, and 85% had nodal involvement, whereas these figures in the Dutch trial were

27% and 55% respectively. Nevertheless, the level of surgical quality control was remarkable low: patients were randomised after surgery, thus leaving no room for any surgical quality assurance: the only surgical requirements were a "resection with curative intent", and a "en bloc resection". This is in sharp contrast to the level of quality control of the radiotherapy part, reflected by as much as 35% of the radiotherapy plans that were adjusted to avoid toxic effects on critical organs. The marginal attention for the surgical part lead to a shocking 54% of cases that did not even have clearance of the N1 tier. Initiators of the trial showed themselves that the level of surgical undertreatment clearly affected survival[83]. This statement was made using a novel measure of adequacy of lymphadenectomy, termed the "Maruyama Index of Unresected Disease". This index reflects the adequacy of lymphadenectomy in relation to the extent of nodal disease. The basis of the index is a computer program, created by Maruyama and colleagues at the National Cancer Center Hospital in Tokyo, that offers a computerized search of Japanese gastric cancer cases. The program requires a number of individualized demographic and tumour-related input variables, after which similar Japanese cases are collected. The output consists of the percentage likelihood of positive lymph nodes at each of the 16 lymph node stations. The program has proven to provide a valid and accurate prediction of nodal involvement in a large German patient population[84]. The index, as defined by Hundahl et al.[83], represents the sum of predictions of nodal disease for the regional stations that have been left unresected by the surgeon. A high Maruyama Index reflects therefore a high level of residual nodal disease. The index was shown to be an independent predictor of survival in the SWOG trial (median 70, range 0 – 429), which forced the investigators to conclude that surgical undertreatment, as observed in this trial, clearly undermined survival. Presently, the Maruyama Index of Disease is being calculated in the Dutch trial, thus assessing the quality of surgery in this patient population that has less advanced disease compared to the US trial patients.

In conclusion for gastric cancer, substantial progress has been made in the treatment of gastric cancer patients, especially in the surgical area. Adjuvant treatment may have a role either preoperative by increasing resectability and thus local control, or postoperatively by eradicating residual (micro)metastatic disease. To our belief, its efficacy must however be tested in relationship with adequate surgery before it may be considered standard therapy. Surgical and pathological quality assurance is key in future prospective randomised trails that will investigate the role of promising novel chemotherapeutics.

3 RECTAL CANCER

3.1 Surgery

Like for gastric cancer, surgery is the key to cure for patients with rectal cancer. The surgical principles in the treatment of colorectal cancer were formulated for the first time at the

beginning of the twentieth century. Until then local recurrences after surgery for rectal cancer occurred in almost 100% of the cases and postoperative morbidity and mortality were substantial. Miles introduced in 1908 a combined abdominal and perineal approach that was initially associated with high operative mortality (42%)[85]. However, in 1923 Miles reported a large series with postoperative mortality dropping to 10% and local recurrences occurring in 30% of the cases[86]. In the same year Hartmann proposed an alternative technique, a two step procedure for cancers located proximally in the rectum: a colostomy was established at the first operation, after which resection of the tumour took place via the abdomen with the distal part of the rectum left behind at the second operation[87]. Sphincter preserving techniques with restoration of bowel continuity were introduced in recent decades. The obvious advantage of anterior resection is the avoidance of permanent colostomy, which may influence patient's quality of life. The introduction of mechanical stapling devices[88] and the observation that a distal resection margin of 2 centimetres can be considered a oncological safe margin[89,90], led to an increased rate of sphincter saving procedures. The downfall in often mutilating abdominal perineal resections and the accompanying definite colostomies can be considered a major advance in the surgical treatment of rectal cancer patients.

Despite these advances, it still remains difficult to obtain local control after surgical treatment, considering the often high rates of local recurrences that vary considerably between institutions[91-95]. It is important to prevent local recurrences as they cause in disabling symptoms like bleeding, pain and faecal incontinence[96] and often lead to death[97]. The narrow anastomotic boarders of the rectum pose the challenge to the surgeons to remove rectal tumours completely from the pelvic area. In an attempt to improve local control and survival, many surgeons have changed their surgical technique in an essential way. The basic conventional surgical technique involving blunt digital dissection, often resulted in incomplete removal of the mesorectal tissue. Resection of the mesorectum is important as this fatty tissue surrounding the rectum often contains non-nodal foci of metastatic disease that are responsible for local failure[98]. Table 1 shows local recurrence after so called curative surgery in conventional surgery series. Rates from 12% up to 38% have been reported. In addition to this lack of local control, damage to the autonomous pelvic nerve plexus is common leading to sexual [98,99] and bladder dysfunction after surgical treatment [100] .

A major breakthrough was achieved with the introduction of Total Mesorectal Excision by Heald at the North Hampshire Hospital in Basingstoke in 1979[101]. It was postulated that local failure was more a result of leaving behind mesorectal tissue than of the inherent nature of rectal cancer. Meticulous dissection under direct vision to envelope and remove the lymphovascular tissue entirely was hypothesized as crucial to avoid local failure. Few years later Quirke et al.[102] showed that local recurrences were more often seen in patients with involved lateral margins, thus unraveling the major mechanism of local recurrence. In a series of 115 consecutive curative anterior resections by Heald, a cumulative risk of local recurrence at 5 years was as low as 3.7%, with an overall survival rate of 87.5%. No patient received

Table 1. Local recurrence after "curative" conventional surgery; adapted from Kapiteijn et al.[15]

Reference	Patients	Local recurrence (n)	Local recurrence (%)	Remarks
Rao '81[148]	204	44	21.6	
Rich '83[149]	142	43	30.3	
Pahlman '84[150]	197	74	37.6	
Phillips '84[92]	848	124	14.6	
Pilipshen '84[151]	382	105	27.5	27% received preop RT
McDermott '85[152]	934	193	20.7	
Pescatori '87[153]	162	19	11.7	
Athlin '88[154]	99	37	37.4	unknown no. of patients received postop RT/CT
Rinnert-Gongora '89[155]	258	53	20.5	
Zirngibl '90[156]	1153	265	23.0	
Akyol '91[157]	294	49	16.7	
Stipa '91[158]	235	42	17.9	
Adam '94[159]	141	32	22.7	6% received postop RT
Nymann '95[160]	175	37	21.1	
Damhuis '97[161]	902	162	18.0	8% received postop RT
Mollen '97[162]	232	42	18.1	27% received postop RT
Kapiteijn '98[91]	668	150	22.5	36% received postop RT
Kapiteijn '02[18]	269	43	16	

adjuvant therapy. Surprised by these excellent results, independent audit was required to convince colleagues of the validity of the data[103]. In the 1980s, Enker in the United States changed his practise to TME and produced similar results to Heald for local control and survival[104-106]. Aitken documented a series of 64 curatively resected TME cases of which only one had a local recurrence[107]. The acknowledgment of the importance of mesorectal excision led to nationwide programs in Europe to introduce TME. The Norwegian Rectal Cancer Project-initiated in 1993- encouraged and taught surgeons to employ TME surgery[17]. Outcome of total mesorectal excision was compared with conventional surgery. The proportion of patients undergoing total mesorectal excision was 78% in 1994, increasing up to 92% in 1997. The observed local recurrence rate for patients undergoing a curative resection was 6% in the group treated by total mesorectal excision and 12% in the conventional surgery group.

Four-year survival rates were 73% after TME and 60% after conventional surgery. In Sweden a similar project was launched[16]. As part of a surgical quality assurance program, workshops were organized that included 11 television-based demonstrations. Pathology quality control consisted of histopathology sessions in order to teach pathologists to identify possible lateral tumour spread. The study population consisted of all patients who underwent TME surgery in the Stockholm County during 1995 and 1996 (n=447). Outcomes at 2 years were compared with those from the Stockholm I (n=790) and II (n=542) trials as historical controls. Local recurrence occurred in significantly fewer of the TME group than of the Stockholm I and II groups (6% vs. 15% and 14%, $p<0.001$) as did cancer-related death (9% vs. 15% and 16%, $p<0.002$). In the Netherlands, TME was introduced within the framework of the "Dutch TME trial" that investigated the efficacy of preoperative short term radiotherapy in TME treated patients. Patients that underwent curative TME surgery without any adjuvant treatment, were compared with patients from an older trial (cancer recurrence and blood transfusion (CRAB)) in which conventional surgery was performed without any quality control[108]. The local recurrence rate decreased from 16% in the CRAB trial after 2 years to 9% in the TME trial ($p = 0.002$) with a higher overall survival after TME (86% vs. 77%, $p = 0.002$)[18].

TME does not only result in improved oncological outcome. By performing surgery under direct vision of the pelvic area, autonomic nerves that are crucial for bladder and sexual functioning, can be identified and spared. Nesbakken et al.[109] reported a series of 39 TME patients that had a remarkable low frequency of serious bladder and sexual dysfunction. Maurer et al.[110] showed that TME offers a significant advantage with regard to preservation of postoperative sexual function in men. Operative procedures for primary rectal cancer from Japan combine pelvic nerve-preserving techniques with radical tumour resection to ensure optimal local tumour control with minimal bladder and sexual dysfunction. In the Netherlands, a prospective study was undertaken to evaluate functional outcome of TME surgery. Forty-seven patients were operated on by a Japanese surgeon who was familiar with nerve preserving TME surgery. Voiding and sexual function were analysed using questionnaire. Three of 11 women and 19 of 30 men were sexually active. Two men were impotent after operation. Impotence was related to sacrifice of the inferior hypogastric plexus ($p = 0.037$). Preservation of the superior hypogastric plexus was crucial for ejaculation ($p = 0.003$).

So TME results in better local control and survival, increased sphincter preservation[111] and improved functional outcome. However, there is some concern about the increased risk of symptomatic anastomotic dehiscence after TME surgery[107,112,113], which may influence local control in negative way according to a recent publication[114]. The increased rates of anastomotic failure probably relate to the rise in sphincter preservation procedures and the consequent higher proportion of patients with distal bowel anastomoses. Also, TME potentially endangers the blood supply to the remaining rectum, thus jeopardizing anastomotic healing. Finally, removing the mesorectum leaves a large pelvic space for accumulation of an infected haematoma, which bears the risk of sepsis. To avoid severe complications

of anastomotic failure like peritonitis, septic shock and even death, it is crucial to take all possible measures to prevent symptomatic anastomotic dehiscence. The most important measures advocated so far is stoma formation[113,115], especially for the low lying rectal tumours[116,117] Again, there is considerable inter-institution and intersurgeon variation with respect to postoperative morbidity and mortality[118-121]. It is remarkable that there is no unanimous policy among surgeons to minimise the risk for the most important surgical complication after rectal cancer surgery, responsible for significant morbidity and mortality[115,122-125]. In our Dutch TME population, anastomotic leakage occurred in 11.8% of the Dutch patients who underwent an anterior resection (n = 924). A protective stoma formation was done in only 57% of the cases. Patients with a stoma had significant less often a anastomotic leakage than patients that did not have a stoma (16.0 vs. 8.2%, p<0.001). Surprisingly, lack of pelvic drains proved to be the most significant risk factor in the multivariate analysis: 23.8% of patients that did not have pelvic drainage developed a leakage compared to 9.6% of the patients with drainage. Considering the wide variation in rates of postoperative complications and surgical procedures, it is necessary to standardise surgical treatment in order to reduce surgical morbidity of TME.

3.2 Adjuvant treatment

Although not practiced yet worldwide, the impact of total mesorectal excision is beyond dispute. Apart from this significant progress in the surgical area, various adjuvant treatment regimens have shown to improve both local control and survival as well. Radiotherapy, either before or after surgery, has been tested in several major trials[126-133]. The rationale of combining surgery with radiotherapy is that surgery is capable of removing tumour bulk whereas radiotherapy kills peripheral malignant cells in well vascularized tissues surrounding the tumour.

It is being heavily debated whether radiotherapy should be given pre- or postoperatively. Postoperative treatment has the advantage of accurate selection of high risk patients, based on histopathological examination and avoids therefore possible under- and overtreatment in contrast to neoadjuvant treatment. However, the only available randomised trial comparing pre- and postoperative treatment clearly showed the superiority of preoperative radiotherapy regarding side effects and local control (local recurrence rates of 12 and 21% respectively, p = 0.02)[134]. In terms of tumour biology, preoperative radiotherapy is to be preferred to postoperative irradiation as tumour cells before surgery have higher oxygen saturation and are therefore more sensitive to irradiation. Furthermore, preoperative radiotherapy devitalises tumour cells that maybe dispersed during the operation, and reduces therefore the risk of metastasis. In the Swedish Rectal Cancer trial it was shown that a short-term regimen of high-dose preoperative radiotherapy (5x5 Gy) administered in one week was capable of reducing local recurrence rates (27 vs. 11%, p<0.001) and improving 5 year overall survival (48% vs. 58%, p = 0.004) compared to surgery alone. The results are in line with a large meta-analysis,

including 8507 patients from 22 randomised trials that concluded that preoperative is superior to postoperative radiotherapy in terms of cancer specific death (45% and 50% respectively, p=0.0003) and reduction of local recurrence risk (46% and 37%, p=0.002)[135]. Moreover, preoperative treatment has clear advantages in terms of compliance, morbidity and financial costs. Despite these clear benefits, the National Institutes of Health guidelines in the USA still recommends combined postoperative chemoradiation in T3, T4 or N+ patients[136]. To guarantee its effectiveness, postoperative irradiation should start not later than 4 tot 6 weeks after surgery to prevent tumour cell proliferation in the postoperative, fibrous and hypoxic tissues. However, many patients turn out not to be fully recovered from the operation at this point in time, which causes a delay in receiving adjuvant radiotherapy. This lack of compliance jeopardises therefore the possible benefits of postoperative radiotherapy.

Another important indication of preoperative radiotherapy is to achieve downstaging and downsizing in order to facilitate complete resection of locally advanced tumours. The level of downstaging correlates with the fraction size and total dose of radiotherapy applied. To allow enough time to for tumours to reduce in size, the interval between the first day of radiotherapy and surgery needs to be at least 4 weeks. The short term regimen of 5 daily fractions of 5 Gy is not suitable for this purpose, since surgery must be performed as soon as possible after completion of this therapy to avoid surgical complications. So irresectable large tumours should be treated with a conventional radiotherapy scheme of 46 to 60 fractions of 2.0 or 1.8 Gy. After a time interval of 4 to 6 weeks the downsized and downstaged rectal tumours can be resected. It is obvious that complete resection of these tumours without neoadjuvant treatment is not feasible.

Concern has been raised on the toxic effects from adjuvant radiotherapy. In the Stockholm I trial there was 8% mortality in the 5x5 Gy arm compared to 2% in the surgery alone arm[126]. In the Imperial Cancer Research Fund trial these rates were 12% and 7% respectivelty[127]. These unacceptable high proportion of treatment related deaths were clearly due to suboptimal treatment techniques: radiotherapy in these trial was delivered by two opposed fields, which increases the volume treated with the prescribed dose considerably. Results of later trials[134,137], employing adequate treatment techniques, demonstrated that daily 5 Gy fractions can be given safely. In the Dutch TME trial, testing 5x5 Gy in TME treated patients, hardly any acute toxicity from radiotherapy occurred.

Late toxicity of radiotherapy has been described by Frykholm et al.[134] who in showed increased rates of bowel obstruction requiring surgery in irradiated patients. Dahlberg et al.[138] showed that short term preoperative radiotherapy in the Swedish Rectal Cancer trial influenced long-term bowel function, considering the high bowel frequency ($p<0.01$), urgency ($p<0.01$), and emptying difficulties ($p<0.05$) in irradiated patients. Finally, Kollmorgen et al.[139] studied the long term effects of postoperative chemoradiation and concluded that this adjuvant regimen had a major long-term detrimental effect on bowel function. With improved radiation techniques, late toxic effects will be less pronounced. Currently, late

morbidity is being analysed in the Dutch TME trial, using questionnaires to be sent to every patient who is disease-free. The possible late toxic effects have to be counterbalanced against the benefits of radiotherapy on both local control and survival. One of the goals should be to give radiotherapy to those patients only who will benefit the most from it. This of course implies accurate pre-treatment staging.

The benefits of (neo-)adjuvant chemotherapy and/or radiotherapy have all been established in the era of suboptimal conventional surgery. With the advent of TME surgery local control and survival have been improved dramatically. Results from experienced centers have been excellent without the application of any adjuvant therapy at all. So, the question had to be answered whether adjuvant treatment has any value in combination with TME surgery. This issue was addressed by the Dutch Colorectal Cancer Group together with the Nordic Gastrointestinal Tumour Adjuvant Therapy Group and the EORTC that initiated a large prospective randomised multicenter trial to investigate the efficacy of preoperative radiotherapy (5x5 Gy) in combination with TME. Standardization and quality control of surgery, radiotherapy, and pathology were achieved by means of a monitoring committee of specially trained instructor surgeons, a panel of supervising pathologists and study coordinators for surgery, radiotherapy and pathology. Surgical techniques were standardised and the participating surgeons attended workshops and symposiums, saw instructional videotapes and were monitored by specially trained surgeons[140]. Pathologists were taught to identify lateral spread of the tumour according to the protocol of Quirke et al.[102]. A total of 1861 patients were randomly assigned to one of the two treatment groups. Before the start of the TME trial, there were doubts whether the excellent results obtained by specialized surgeons could be matched in a large multicenter trial. There was a low rate of local recurrence after 2 years (8.2%) in the group assigned to surgery alone.[141] This figure indicates that general surgeons, who are adequately trained in the TME surgery, can achieve similar excellent results.

In the Dutch TME trial, preoperatively irradiated patients had an even lower risk of local failure (2.4%) after a median follow-up of 2 years than patients who underwent surgery alone, thus proving that radiotherapy has a value for local control, even when combined with TME surgery. There was no significant difference in survival (82.0% vs. 81.8%, p=0.84). Complete tumour removal proved to be crucial in attempt to prevent local failure. Circumferential margin (CRM) involvement was a strong predictor, independent from TNM classification, for local recurrence: a resection margin of 2 millimetres or less was associated with a local recurrence risk of 16% compared with 6% in patients with more mesorectal tissue surrounding the resected specimen ($p < 0.0001$)[142]. Apart from margin involvement, determination and reportage of the completeness of the mesorectum have proved to be a strong instrument to predict recurrent disease: patients with an incomplete mesorectum had an increased risk for overall recurrence: 36.1% versus 20.3% in the group with a complete mesorectum ($p = 0.02$).[143] This macroscopic direct evaluation of surgery is very informative to the

individual surgeon and can serve as a good tool to audit and subsequently improve surgical performance.

Despite surgical and pathological quality assurance, 18% of the TME treated patients had a positive margin (i.e. 1 millimeter or less), which clearly increased the risk of both local and distant recurrence. So, there is still room for further improvement. Involvement of radiologists may aid in avoiding non-curative resections. MRI provides clear imaging of the surgical plain of dissection and the adjacent tumour deposits. Beets et al.[144] showed that the circumferential resection margin can be predicted with high accuracy and consistency, allowing preoperative identification of patients at risk for unsuccessful tumour clearance. The Pelican Mercury study[145] that compares pretreatment MRI staging with pathological staging in underway and will most likely stress the importance multidisciplinary teams planning multimodality treatment. Establishing a complete resection is crucial as, in the Dutch TME trial, preoperative irradiation had only limited effect in reducing the local recurrence risk in patients with positive margins (9.3% vs. 16.4%, $p = 0.08$). Neither could postoperative radiotherapy prevent local failure in these patients (17.3% vs. 15.7%, $p = 0.98$).[146] In other words, adjuvant radiotherapy can only partly compensate for suboptimal surgery. This underlines once more the importance of "good" surgery.

So based on the results from the Dutch TME trial one may conclude that the problem of local failure has been adequately tackled by both TME surgery and preoperative short term radiotherapy. Survival however, needs to be further improved with an increased proportion of patients dying from distant/liver metastases. Systemic therapy may be of use in an attempt to improve survival, like it is the case in stage III colon cancer. In earlier years, postoperative chemotherapy has been tested in a prospective trial by Taal et al.[147]: there was no significant and disease-free survival benefit from adjuvant 5 FU plus levamisole in rectal cancer patients, possibly due to the fact that there were relatively few rectal cancer patients (n=299), but most likely also due to the 23% of patients with local recurrences, being an important cause of death. One may hypothesize that this high rate of local failure blurred the beneficial effect of chemotherapy on survival. The successor of the Dutch TME-trial, the PROCTOR (Preoperative Radiotherapy and/Or adjuvant Chemotherapy combined with Tme-surgery in Operable Rectal cancer) trial is currently investigating the additional value of postoperative chemotherapy (5-FU/Leucovorin according to Mayo or Nordic regime) in stage II and III rectal cancer patients. The overall survival in the arm treated without chemotherapy is expected to be 60%. Assuming that postoperative chemotherapy leads to an improvement in overall survival from 60 to 70%, 500 patients are needed per arm.

As adjuvant treatment improves with the introduction of superior radiotherapy techniques and novel chemotherapeutic agents, surgical technique has changed dramatically. The data for the superiority of mesorectal excision over conventional surgery are overwhelming. However, adoption of surgical and pathological concepts arising from TME surgery has been remarkably slow so far. Blunt digital dissection is still reported in a 2002 United States surgical

textbook, describing the "sucking noise" when removing the rectum bluntly. When costly and only marginally effective chemotherapy regimens are swiftly introduced into clinical practise, it is astonishing that TME surgery, that has been shown to improve local control, survival, nerve and sphincter preservation dramatically, is not implemented systematically by health care providers. From quality assurance point of view, it is crucial to expand TME surgery beyond the boarders of clinical trials, like it has been done in Norway[17]. Considering its impressive superiority, we believe TME cannot longer withheld from rectal cancer patients. Adjuvant treatment is generally accepted as valuable, but should be tested in combination with TME surgery. Initiators and participants of future trials should embrace the challenge of involving radiologists and pathologists to design new studies with adequate quality control. Only in this way, factors can be identified that may determine patients' prognosis significantly, like inadequate surgery and/or pathological examination. This approach will not only result in improved surgical treatment, but will provide a more reliable assessment of the benefits of adjuvant treatment as well.

4 CONCLUSION

Quality assurance comprises all systematic measures leading to quality controlled diagnosis, pre-treatment staging and multimodality treatment of cancer patients. Large scale surgical quality assurance programs have proven to be feasible and result in significant improved treatment outcome compared to historical controls. Surgery is the main discipline responsible for cure in both gastric and rectal cancer. Therefore, investing in the quality of surgery will yield a substantial profit. This is not only important for cancer patients, but also for all medical professionals who are willing to optimise multidisciplinary treatment and to test new promising treatment regimens in combination with optimal surgery.

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