

Is sphincter saving an important end-point?

Lars Pålman

Department of Surgery, University Hospital, Colorectal Unit, SE-751 85 Uppsala, Sweden

Introduction

Loco-regional tumor control in rectal cancer surgery has changed dramatically during the past 10–15 years and started with the discussions of the value of more exact surgery and precise procedures following the embryonic planes. This surgical technique is nowadays called a Total Mesorectal Excision (TME) [1]. By using this technique, locally radical surgery can easily be achieved without compromising the sphincter function in patients with a tumor in the upper and middle third of the rectum. This rationale is derived from the knowledge that a rectal cancer rarely grows more than a few millimeters distally from the macroscopic margin, indicating that a distal margin of 1 cm will probably be sufficient for local cure in terms of intramural spread [2]. However, lymph node deposits in the mesorectum can be found up to 4 cm distally from the tumor [3,4]. In analogy with this finding, in tumors in the upper third of the rectum, the mesorectum has to be divided at least 5 cm from the macroscopic tumor edge if a division of the mesorectum is planned. In patients with a tumor in the middle or distal third of the rectum, a TME is always indicated if the 5 cm rule is to be followed. Subsequently, in the lower third of the rectum a distal macroscopic margin of 1 cm is enough after a TME, as long as the dissection follows the embryonic planes and the cancer is not growing outside the fascia envelope of the mesorectum. In those situations the sphincter function can be preserved with an anastomosis created to the top of the anal canal.

Therefore, the crucial point regarding sphincter preservation is the situation with a tumor in the lower third of the rectum. Since mesorectum is decreasing in size closer to the top of the anal canal, tumors arising in this area can rather easily invade the surrounding structures, like the internal and external sphincters. If the size of the tumor exceeds a T2-tumor this is by definition a reality. Consequently, it is crucial to have the pelvic floor free from tumour if a loco-regional curative procedure is to be performed in very low rectal cancer.

It has been claimed, mainly based upon historical controls, that radiotherapy, and preferably chemo-radiotherapy with delayed surgery will increase the number of preserved sphincters due to a downsizing effect on the tumor by induction treatment.

Changes in surgical philosophy

Sphincter preservation for rectal cancer started in the late 1940s and early 1950s, when it was obvious that rectal excision could be performed with a primary anastomosis [5]. Before that, philosophy was that rectal cancer was spread distally outside the pelvic floor [6]. Apparently, this hypothesis of tumor spread was wrong and therefore an anterior resection has become more and more popular. As the anastomosis deep in the pelvis is rather tricky, a real change in increasing number of sphincters preserved became obvious when the stapling technique was available in the mid 1970s [7]. Since then it is obvious from institutional series, different randomized trials and national registers that the number of patients with preserved sphincters has increased from 25% up to 50–60% [8]. Moreover, there are centers of excellence, where the number of patients with preserved sphincters is as high as 90%, although it is always difficult to interpret those data due to selection bias and case mix [7]. Based upon prospective population-based registration from several national cancer registers, the proportion of patients in the total population having a sphincter-preserving procedure is around 50% [8,9].

An interesting phenomenon is how the modern way of using radiotherapy in a neoadjuvant setting has further changed the philosophy, and many surgeons presently claim that more sphincters can be preserved, provided that preoperative chemo-radiotherapy is used. Unfortunately, there are very few randomized trials supporting this idea [10]. When comparing new data with historical controls, one has to take into account the main change in rectal cancer surgery during the past 10–15 years. As mentioned above a 1 cm margin is now considered good surgery compared with the

Table 1

The change in number of preserved sphincters from four different trials including patients during the 1980s and 1990s. All trials used short-course radiotherapy and immediate surgery

Time period	Trial	Numbers	Surgery alone	Preop. irradiation
1980–1985	Uppsala [11]	471	33%	34%
1980–1987	Stockholm I [12]	849	36%	36%
1987–1990	SRCT [13]	1154	41%	44%
1996–1999	Dutch trial [14]	2188	67%	65%

Table 2

Sphincter preservation in six trials with preoperative radiotherapy and delayed surgery compared to immediate surgery, chemoradiotherapy or surgery alone, respectively

Trial	Type of treatment	preserved sphincters	p-value
Lyon [15]	Preop. irradi., immediate/delayed surgery	68%/76%	ns
Polish [16]	Preop. chemorad./preop. short-course	58%/61%	ns
EORTC [17]	Preop. chemorad./preop. irradi.	56%/53%	=0.05
French [18]	Preop. chemorad./preop. irradi.	52%/52%	ns
NSABP [19]	Preop. chemorad./postop. chemorad.	44%/34%	ns
German [20]	Preop. chemorad./postop. chemorad.	69%/71%	ns

standards 15 years ago when the 5 cm rule was used. Therefore, comparing series from this decade with series from the 1980s and 1990s will inevitably show more preserved sphincters now than then. Whether this change has anything to do with the preoperative chemo-radiotherapy is actually not known; rather the change in surgical attitude is more important than the effects of any preceding radio-(chemo)therapy.

Radiotherapy and sphincter preservation

The prerequisite for a downsizing effect of radiotherapy is to prolong the time from the end of the radiotherapy to the surgery. In all trials where radiotherapy has been followed by immediate surgery there has been no effect on the sphincter preservation rate. However, it is obvious that the change in surgical practice can be seen in the four large randomized trials [11–14] including patients from the 1980s and 1990s using short-course preoperative radiotherapy with immediate surgery (Table 1).

There are seven trials recently published with different types of radiation schedules, where sphincter preservation can be evaluated (Table 2). In two of the trials, the Lyon, R90-01 trial [15], and the

Polish trial [16], sphincter preservation was specifically addressed. In the French trial [17] and the EORTC trial [18] preoperative chemoradiation was compared to preoperative radiotherapy alone. In the NSABP trial [19] and the German trial [20] preoperative chemoradiation was compared to postoperative chemoradiation, giving the opportunity to compare surgical outcome from preoperative chemoradiation with no preoperative treatment. Finally, one trial from Lyon studied external beam therapy alone versus external beam irradiation + endocavitary irradiation [21].

In the Lyon trial sphincter preservation was the main endpoint [15]. Two hundred and one patients with T2–T3 tumors were treated with 39 Gy delivered in 13 fractions during 17 days. After completed radiotherapy, patients were randomized to surgery after 2 weeks or after 6 to 8 weeks. Despite a better pathologic downstaging (10% vs 26%, $p=0.005$), only a trend for more preserved sphincters could be seen after the prolonged interval from radiotherapy to surgery (76% vs 68%, $p=0.27$). The overall local recurrence rate in this trial was 9%. However, an important observation from the Lyon trial is the increase in local recurrence rate from 9% to 12% in the group of patients where the surgeon changed from

an abdominoperineal excision (APR) to a sphincter-preserving procedure [15].

In the Polish trial, 311 patients were randomized to receive either short-course 5×5 Gy followed by immediate surgery or long-course preoperative chemoradiotherapy during 5 weeks followed by surgery 5–7 weeks later [16]. Inclusion criteria were T3 or mobile T4 tumors reachable with a digital examination; however, without infiltration of the sphincters. Moreover, a distal margin of 1 cm was accepted. In this trial the surgeon should state before radiotherapy whether or not a sphincter-preserving procedure was possible. As shown in Table 2 there is no improvement in sphincter preservation after preoperative chemoradiotherapy and delayed surgery. So far, oncological outcome like local recurrences and cancer-specific survival has not been reported.

An important question whether additional chemotherapy to the preoperative radiotherapy will increase sphincter preservation was addressed in two recently published trials, the EORTC 22921 trial [17] and the French FFCD 9203 trial [18]. The primary endpoint in both trials was survival and sphincter preservation was a secondary end point. In both trials exactly the same chemotherapy was used (5-FU $350 \text{ mg/m}^2/\text{day}$ i.v. bolus + folinic acid $20 \text{ mg/m}^2/\text{day}$). Among the 1011 patients in the EORTC trial an increased rate of complete pathological response was seen after combined treatment (14% vs 5%). The FFCD-trial included 762 patients, and the corresponding figures were 11% vs 3%, respectively. An increase in preserved sphincters could not be seen in any of the two trials despite this marked increase in number of complete pathological response to chemoradiotherapy (56% vs 53%, EORTC and 52% vs 52%, FFCD) (Table 2).

In the NSABP protocol R-03 [19] and the German CAO/ARO/AIO trial [20] patients were randomly allocated to preoperative chemo-radiotherapy and delayed surgery or postoperative chemo-radiotherapy with similar technique. In both trials 5-FU and folinic acid was used, and surgery in the neo-adjuvant arm was performed after approximately 6-weeks. Since the postoperative arm is untreated before surgery a perfect comparison between neo-adjuvant chemoradiotherapy and delayed surgery versus surgery alone can be done. The NSABP trial was closed when only 267 out of planned 900 patients were included due to recruitment problems, giving an underpowered trial. Therefore, the figures regarding sphincter preservation must be taken with caution (Table 2).

In the German trial 823 patients were included [20]. A similarly good effect on complete response to

neo-adjuvant chemo-radiation could be seen (8%). The overall proportions of patients with sphincter-preservation in both groups were the same (69% vs 71%). However, in a subgroup of patients with low-lying tumors, the surgeons estimated preoperatively that an APR was necessary. Although difficulties to figure out exactly how this sub-group is constituted exist, this cohort of patients had more sphincters preserved if neo-adjuvant chemoradiotherapy was given (45/116, 39% vs 15/78, 19%; $p=0.004$).

In the Lyon R96-02 protocol external beam radiotherapy alone (39 Gy in 13 fractions) was tested in a randomized fashion against the same external treatment + contact radiotherapy boost of 85 Gy in 3 fractions [21]. In total, 88 patients with a low-lying T2 or T3 tumor were included in the trial. In the combined group a complete response was seen in 29% (13/49 patients) compared to 2% (1/43) in the external radiotherapy group alone. The corresponding figures for sphincter preservation were 78% and 44%, respectively ($p=0.004$). Local recurrence rate and overall survival were similar in the two groups after 2 years [21].

Quality of life

Technically, there are no problems performing a very low anastomosis using the intersphincteric technique of dissection with an anastomosis down to the dentate line. With such low anastomoses many patients will have real problems with sphincter function. Based upon reports, most patients are considered to have an acceptable to good function but as many as 20% will be more or less incontinent, not only for flatus or loose stool but also for solid stool [21]. It is apparently very difficult to interpret the literature on this topic, as the cultural differences are enormous. It appears as if a colostomy is more or less a disaster to the patient and also a failure for the surgeon in the southern part of Europe and in the Arabic world. Therefore, many patients from the Mediterranean areas do accept a poor bowel function instead of a stoma and also accept using diapers. In the northern part of Europe, however, it is the clear impression that a stoma is not such a disaster and data support that a stoma often is a better alternative in rectal cancer surgery than a non-optimal bowel function. Based upon questionnaire studies stoma patients, as a group have not a worse quality of life than patients treated with sphincter preservation [22].

The use of radiotherapy definitely diminishes the risk of local recurrence [10] and has been quoted to

increase the number of preserved sphincters. However, there is strong evidence from literature that the bowel function will be deteriorated after both preoperative [23,24] and postoperative irradiation [25,26]. Moreover, the real long-term effects of radiotherapy are difficult to foresee. In analogy with patients having had radiotherapy for anal or prostate cancer the sphincter function may deteriorate up to at least 10–15 years after treatment [27,28]. Therefore, the evidence of using radiotherapy or chemoradiation just to preserve more sphincters is weak, and the adverse effects can ultimately destroy an initially good outcome.

In almost all cases with a very low anastomosis, some type of colonic reservoir construction is necessary to improve bowel function [29–32]. In cases when the whole sphincter area has to be excised the destroyed sphincters can be restored by the use of a stimulated graciloplasty. The sigmoid colon is placed as a perineal stoma and the gracilis muscle is wrapped around the bowel as a neo-sphincter, which can be stimulated with a pacemaker, and, in such a way, act as a continent sphincter. In essence, the patients will be left with a perineal stoma and the sphincter function will be supported by this stimulated graciloplasty. Preliminary reports were very optimistic, but after a longer follow-up it is obvious that those patients do not have a normal life. They need enemas to evacuate the bowel and all of them need a pad due to soiling [33–36].

A common technique today to make the stoma care more convenient for the patients is to use a retrograde irrigation system, where the patients are emptying the bowel every second or third day using an enema. By doing so, just a pad is needed to cover the stoma instead of stoma bag [37].

Conclusions

The main goals in rectal cancer surgery are to achieve a curative procedure in terms of loco-regional control and an overall high chance to survive. Of relevance, is also to perform all treatments so that the well being/quality of life can be as good as possible. Sphincter preservation has become a new end-point and it has been claimed that more sphincters can be preserved if neoadjuvant chemoradiotherapy is used. Based upon randomized trials, the evidence does not support this philosophy. Moreover, the addition of radiotherapy will in the long run deteriorate the sphincter function.

With modern surgical technique and new acceptance of a short distal margin, very low anastomoses into the

intersphincteric area can be done. The question, is if such a procedure should be done without taking into account bowel function, since the patients' sphincter status is of outmost importance and will have an impact on functional outcome. If a patient has had an injured sphincter or has IBS problems, a preserved sphincter can actually be a disaster for the patient. In such a case, even if it is technically possible to perform an anterior resection despite a bad sphincter function, a Hartmann's procedure is a better choice. Such an operation is in this specific situation superior to an abdominal perineal excision, since the perineal wound healing will not be impaired.

In summary, sphincter preservation cannot be a valid endpoint in rectal cancer surgery. Moreover, according to the present knowledge preoperative chemoradiotherapy does not increase, or only marginally so, the number of preserved sphincters.

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