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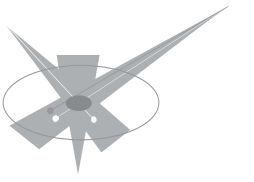

Original Paper

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Neoadjuvant radiotherapy and anastomosis dehiscence after total mesorectal excision for stage II and III rectal cancer

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A Study Design
B Data Collection
C Statistical Analysis
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Summary

Background Anterior resection is nowadays the preferred option of surgical treatment for rectal cancer without sphincter involvement. However, this operation is associated with the risk of anastomosis dehiscence (AD).

Aim The aim of this study was to estimate the influence of neoadjuvant radiotherapy and other factors on the risk of anastomosis dehiscence after total mesorectal excision for stage II and III rectal cancer.

Materials/Methods One hundred and thirty consecutive patients operated on due to histologically confirmed rectal carcinoma were studied with prospective data collection. Elective surgery with curative intent was administered. All patients underwent sphincter-sparing anterior resection with total mesorectal excision. End-to-end anastomosis with double stapled technique was performed. Impact of patient-, tumour- and treatment-related variables on anastomosis dehiscence rate was evaluated in univariate and multivariate analysis.

Results Incidence of AD was 10.6%. There was no leakage-related mortality. Univariate analysis showed that patient's age and gender, presence of lymph node metastases and irradiation setting (pre- vs post-operative) did not significantly influence dehiscence rate ($P>0.05$). Tumour level at or below 7cm from the anal verge was related to increased AD risk with statistical importance ($P=0.0438$). Neither pelvic drainage nor omentoplasty effectively protected the anastomosis. Proximal diversion with protective stoma resulted in significantly decreasing AD risk ($P=0.0012$). In multivariate analysis the presence of transversostomy was found as the most important factor independently associated with significantly lower incidence of AD.

Conclusions Neoadjuvant radiotherapy does not seem to be a significant risk factor for anastomosis dehiscence, even after resection of low-sited tumours, but proximal diversion with temporary stoma needs to be considered.

Key words **rectal cancer • total mesorectal excision • neoadjuvant radiotherapy • anastomosis dehiscence**

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Background

In the year 1990 combined postoperative chemoradiation as adjuvant treatment for rectal cancer was recommended by the National Institute of Health [1]. At the end of the last century results of the Swedish Rectal Cancer Trial suggested oncological benefits of preoperative short-term hypofractionated high-dose irradiation [2]. These advantages were thereafter confirmed in other prospective studies [3,4] and randomised multicentre trials [5,6]. Neoadjuvant radiotherapy 25Gy in five daily fractions of 5Gy can decrease local recurrence risk by 50–70%, enhance long-term survival by 10%, and increase resectability and sphincter preservation rates [7]. Because of the short treatment time, early operation, relatively low cost and patient comfort this radiation schedule became a widely adopted procedure. However, in experimental studies in animal models performed in the eighties anastomotic dehiscence (AD) rates of up to 80% were noticed when preoperative radiation was given [8–11]. The clinical impact of neoadjuvant radiotherapy on the risk of anastomotic dehiscence in rectal cancer patients is still unclear and remains a matter of debate.

Aim

The aim of the study was to evaluate the incidence of clinically symptomatic AD following anterior resection with TME with and without preoperative radiotherapy for stage II and III rectal cancer and to estimate the association of AD rate with patient-, tumour- and treatment-related variables in uni- and multivariate analysis.

Material and methods

Patients

From 01.2000 to 12.2003 at the Second Department of Surgical Oncology of the Lower Silesian Oncology Centre, 130 patients with rectal adenocarcinoma underwent anterior resection fulfilling the selection criteria: tumour sited maximum 12cm from the anal verge, absence of distant metastases, absence of macroscopic infiltration of adjacent organs, distal and radial R0 margins, lack of intra-operative bowel perforation, total integrity of doughnuts after retrieval of the stapler, complete integrity of the anastomosis during intra-operative testing. Ninety-four of them at UICC stages II and III received radiation and chemotherapy and entered the study. The stage was established with preoperative endorectal ultrasound (tumour direct penetration beyond the bowel wall without enlarged lymph nodes was considered stage II, presence of enlarged lymph nodes at the mesorectum suggesting tumour involvement was regarded as stage III) and confirmed by histological examination of the resected specimen. For patients in stage I adjuvant therapy was not administered and they were treated with surgery alone. Therefore, they were not enrolled for the study. Patients underwent pre-operative bowel preparation with 4L polyethylene glycol solution and administration of prophylactic antibiotics.

Surgical procedures

Vessel ligation before intestine preparation was done. Resection was performed according to TME technique, with sharp dissection under the

direct vision of the avascular plane between parietal and visceral pelvic fascia. Special effort was made for adequate colon mobilisation. End-to-end anastomosis with double-stapling technique was constructed. The rectum was transected with the transverse stapler Proximate TLH 30 (Ethicon Endo Surgery Europe, Norderstedt, Germany). Circular intraluminal stapler Proximate ILS (Ethicon Endo Surgery Europe, Norderstedt, Germany) was introduced transanally and fired with the guidance of the abdominal surgeon. Intestine wash-out was made by povidone iodine. Anastomosis integrity was examined by transanal air insufflation of the bowel immersed in saline solution.

Radiation and chemotherapy

Radiotherapy was delivered by linear accelerator (6–18MV). All patients received whole pelvic radiation by three fields (two laterals and one posterior). The lateral fields covered the sacrum and coccyx posteriorly and the femoral head anteriorly. The dose was prescribed to the 95% isodose line. Wedges of different degrees were employed over the lateral fields to homogenize the isodose distribution. The isodose distribution was designed by 2D treatment planning system. Forty-nine patients received preoperative five-day scheduled high-dose hypofractionated radiation with a total dose of 25Gy in daily fractions of 5Gy. The upper limit of all the pelvic fields was at the L5-S1 level and the lower one was 5cm below the tumour. Radiotherapy was followed by surgery within 7 days and postoperative chemotherapy with 5-fluorouracil (325mg/m^2) and folinic acid (20mg/m^2) in six five-day courses with two-hour bolus injection. Forty-five patients received combined postoperative radiochemotherapy. For them radiation was delivered in traditional 25 daily fractions of 1.8Gy over five weeks to the total dose of 45Gy followed by a boost to the primary tumour site with 2cm margins of up to 50.4Gy. Chemotherapy with 5-fluorouracil (325mg/m^2) and folinic acid (20mg/m^2) by intravenous bolus injection was given also in six five-day courses. The two first courses were administered before radiation, the third and fourth were performed concomitantly in the first and fifth week of radiotherapy, respectively, and the last two courses were given after radiation.

Dehiscence diagnosis

AD was considered to be present if any of the following features were noticed: presence of peritonitis caused by anastomotic dehiscence, presence of feculent substances and gas from the pelvic drain, or presence of pelvic abscess with the demonstration of leakage by transrectal examination, endoscopy, contrast enema, endorectal ultrasound or CT scanning.

Risk factors and protection methods

Apart from neoadjuvant radiotherapy, gender (female n=46, male n=48), age (range 33–89 years; mean x=60.6±10.3, median M=61; ≤60 years n=53, >60 years n=41), stage (II n=59, III n=35) and tumour distance from the anal verge (P≤7 cm n=38, >7 cm n=56) were regarded as factors with a possible impact on the AD risk. Operative procedures potentially protecting the anastomosis involved: defunctioning transversostomy (n=62, lack n=32), wrapping the anastomosis with omentum (n=26, lack n=68) and pelvic no-suction drainage (n=55, lack n=56).

Statistical analysis

All data were prospectively collected. Statistical analysis was performed with the computer program set EPIINFO Ver. 3.2. All data were entered into the computer database. Univariate analysis was performed with Pearson's chi-square test with Yates' correction. Odds Ratio (OR) and Relative Risk (RR) with 95% confidence intervals (95% CI) were calculated. For multivariate analysis the logistic regression model (quasi-Newton estimation) was used. P value <0.05 was considered statistically significant.

RESULTS

There was no post-operative or dehiscence-related death. Symptomatic AD was noticed in 10 cases, giving a rate of 10.6%. AD developed in 12% of patients (n=6 of 49) preoperatively irradiated and 9% of patients (n=4 of 45) without neoadjuvant radiotherapy. The difference was not significant (P=0.5981; OD=1.430, 95%CI 0.376–5.438; RR=1.378, 95%CI 0.415–4.568). Five patients with preoperative radiation and AD (83%) had low-sited tumour. None of them had protective stoma. All irradiated patients with proximal diversion independently of tumour level were free of symptomatic AD.

Among patients who developed AD, 6 were effectively treated conservatively (total parenteral nutrition, antibiotics, abscess drainage with the guidance of radiology). The other 4 patients

Table 1. Risk factors for anastomosis dehiscence.

Risk factor	Option	n	AD	P	OR	95% CI	RR	95% CI
Patient's gender	Male Female	48 46	10% 11%	0.9432	0.953	0.257–3.539	0.958	0.297–3.093
Patient's age	>60 ≤60	41 53	12% 9%	0.6668	1.333	0.359–4.955	1.293	0.401–4.168
UICC stage	II III	59 35	10% 11%	0.8482	0.877	0.230–3.353	0.890	0.270–2.937
Radiation therapy	Preop Postop	49 45	12% 9%	0.5981	1.430	0.376–5.438	1.378	0.415–4.568
Tumor level	≤7cm >7cm	38 56	18% 5%	0.0438	3.989	0.961–16.558	3.439	0.948–12.470
Defunctioning stoma	Absent Present	32 62	25% 3%	0.0012	10.000	1.979–50.542	7.750	1.747–34.375
Pelvic drainage	Absent Present	29 65	10% 11%	0.9509	0.956	0.229–3.993	0.961	0.267–3.454
Omental wrapping	Absent Present	68 26	10% 12%	0.8611	0.880	0.209–3.695	0.892	0.249–3.192

n – number of patients; AD – rate of anastomosis dehiscence; P – significance level; OR – Odds ratio; RR – relative risk; 95% CI – 95% confidence interval; Preop – preoperative; Postop – postoperative.

underwent relaparotomy: 3 of them required a diversion stoma with anastomosis preservation, one developed total dehiscence of the anastomosis and required Hartmann's procedure. Preferred time of stoma closure was 12 weeks after primary operation. Bowel reconstruction following Hartmann's resection was successful.

AD rate was higher in patients older than 60 years, in females and in stage III tumours but without statistical significance. The only clinical parameter significantly related to enhanced AD risk was tumour localisation at 7cm or below from the anal verge (P=0.0438; OD=3.989, 95%CI 0.961–16.558; RR=3.439, 95%CI 0.948–12.470).

From surgical procedures neither pelvic drainage nor omentoplasty significantly influenced AD risk. In contrast, the presence of protective stoma was associated with lower AD rate and effectively protected patients from symptomatic AD with statistical importance (P=0.0012; OD=10.000, 95%CI 1.979–50.542; RR=7.750, 95%CI 1.747–34.375).

In multivariate analysis the most important statistically significant factor that independently influenced lower risk of AD was the presence of proximal diversion with temporary stoma (P=0.00735; OD=10.186, 95%CI 2.017–59.743; RR=8.073, 95%CI 1.845–37.914).

Data are shown in Table 1.

Discussion

In our study the only significant clinical parameter was the localisation level of rectal malignancy. Increased AD risk after resection of low-sited tumours (below 5–7cm from the anal verge) was often observed and seems to be well documented [12–14]. We found that proximal diversion by temporary stoma significantly decreased the risk of symptomatic AD. Similarly, in recent papers [12,15], but not in all of them [13], its effectiveness for anastomosis protection was emphasised. The results of a large multi-centre German trial confirmed that defunctioning stoma can reduce the AD risk and decrease the rate of AD requiring surgery due to severe consequences of leakage [16]. Thus, in spite of the high cost, risk of stoma-related complications and low acceptance by patients the use of proximal diversion seems to be valid in cases with low anastomoses, especially when other AD risk factors are present.

In our series AD did not occur significantly more often after neoadjuvant radiotherapy. In contrast, other authors noticed enhanced AD rates when preoperative radiation was given [17–19]. Vermeulen et al. reported that compared with surgery alone, preoperative short-term radiotherapy

significantly increased the number of AD (41% vs 4%, p=0.006) whether or not protective stoma was performed [20]. Analysis of a random sample from all rectal cancer patients in Sweden operated on from 1987 to 1995 showed that short-term radiation was an independent AD risk factor [13]. High-dose preoperative radiotherapy impairs leukocyte production, increases postoperative infective complication rate and significantly reduces collagen concentration in infected patients [21]. On the other hand, similarly to us, investigations of the Dutch Colorectal Cancer Study Group did not reveal a significant impact of neoadjuvant radiation on AD rate [22,23]. The results of a Polish randomized trial suggest that 5×5 Gy radiotherapy is not less effective than long-term radiation for sphincter preservation [24]. Bujko et al. observed that short-course irradiation was not associated with enhanced risk of postoperative morbidity [25] and radiation toxicity [26] when compared to conventionally fractionated radiochemotherapy.

The findings of recent experimental studies are also discrepant. Milsom et al. noticed more frequent AD in animals irradiated before surgery to a total dose of 42.5Gy (29% vs 8%, p<0.05) [27]. Preoperative radiation resulted in enhanced gross and microscopic inflammatory scores [27], reduced perianastomotic blood flow [27,28], significantly decreased local collagen concentration and hydroxyproline content [29]. In other series anastomosis healing was not compromised by preoperative radiation [30,31]. Some suggest that radiotherapy does not influence the anastomosis outcome but may delay the normal healing process [32,33]. In clinical practice only the distal limb of the anastomosis consists of irradiated bowel (rectal remnant) while the proximal limb is not irradiated (colon). De Meerleer et al. reported that compared to non-irradiated bowel the anastomosis strength of unilaterally radiated colorectal anastomosis was not altered but in the case of bilaterally irradiated bowel it was significantly reduced and dose-dependent [34]. Other authors also observed that preoperative radiation of 25–80Gy did not affect the clinical, mechanical, histological and biochemical features reflecting anastomosis healing: pelvic abscess and peritonitis rate, bursting pressure, epithelial regeneration, collagen concentration and hydroxyproline content, respectively [35–38].

For optimal combined-modality treatment planning, risk-benefit analysis should be considered. It has to be remembered that hypofractionated radiotherapy may increase the incidence of urogenital complications, faecal incontinence and other bowel dysfunction. Because of radiation-related complications and side effects the monolithic approach to apply the same schedule of radiotherapy for all patients with stage II and III rectal cancer is questioned by some [39]. Further studies are needed for more accurate identification of patients requiring adjuvant therapy.

Conclusions

1. Neoadjuvant radiotherapy does not seem to influence the anastomosis dehiscence rate after total mesorectal excision for rectal carcinoma.

2. Risk of dehiscence is significantly related to low site of the primary tumour.

3. Effective anastomosis protection can be achieved using proximal diversion with defunctioning temporary stoma.

References:

1. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA ,1990; 264: 1444–50
2. Swedish Rectal Cancer Trial: Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med, 1997; 336: 980–7
3. Delaney CP, Lavery IC, Brenner A et al: Preoperative radiotherapy improves survival for patients undergoing total mesorectal excision for stage T3 low rectal cancer. Ann Surg, 2002; 236: 203–7
4. Holm T, Johansson H, Rutqvist LE, Cedemark B: Tumour location and the effect of preoperative radiotherapy in the treatment of rectal cancer. Br J Surg, 2001; 88: 839–43
5. Wiggers T, van de Velde CJ: The circumferential margin in rectal cancer. Recommendation based on the Dutch Total Mesorectal Excision Study. Eur J Cancer, 2002; 38: 973–6
6. Kapiteijn E, Marijnen CA, Nagtegaal ID et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med, 2001; 345: 638–46
7. Glimelius B, Gronberg H, Jarhult J et al: A systematic overview of radiation therapy effects in rectal cancer. Acta Oncol, 2003; 42: 476–92
8. Morgenstern L, Sanders G, Wahlstrom E et al: Effect of preoperative irradiation on healing of low colorectal anastomoses. Am J Surg, 1984; 147: 246–9
9. Meese DL, Bubrick MP, Paulson GL et al: Safety of low anterior resection in the presence of chron-

ic radiation changes in dogs. Dis Colon Rectum, 1986; 29: 22–6

10. Bubrick MP, Rolfsmeyer ES, Schauer RM et al: Effect of high-dose and low-dose preoperative irradiation on low anterior anastomoses in dogs. Dis Colon Rectum, 1982; 25: 406–15
11. Shauer RM, Bubrick MP, Feeney DA et al: Effect of low-dose preoperative irradiation on low anterior anastomosis in dogs. Dis Colon Rectum, 1982; 25: 401–5
12. Law WL, Chu KW: Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg, 2004; 240: 260–8
13. Matthiessen P, Hallbook O, Andersson M et al: Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis, 2004: 6: 462–9
14. Nesbakken A, Nygaard K, Westerheim O et al: Audit of intraoperative and early postoperative complications after introduction of mesorectal excision for rectal cancer. Eur J Surg, 2002; 168: 229–35
15. Peeters KC, Tollenaar RA, Marijnen CA et al: Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg, 2005; 92: 211–6
16. Marusch F, Koch A, Schmidt U et al: Value of a protective stoma in low anterior resections for rectal cancer. Dis Colon Rectum, 2002; 45: 1164–71
17. Valero G, Lujan JA, Hernandez Q et al: Neoadjuvant radiation and chemotherapy in rectal cancer does not increase postoperative complications. Int J Colorectal Dis, 2003; 18: 495–9
18. Lele S, Radstone D, Eremin J et al: Prospective audit following the introduction of short-course preoperative radiotherapy for rectal cancer. Br J Surg, 2000; 87: 97–9
19. Sauer R, Fietkau R, Wittekind C et al: Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis, 2003; 5: 406–15
20. Vermeulen J, Lange JF, van der Harst EP: Impaired anastomotis healing after preoperative radiotherapy followed by anterior resection for treatment of rectal carcinoma. S Afr J Surg, 2006; 44(12): 14–6
21. Johnson LB, Jorgensen LN, Adawi D et al: The effect of preoperative radiotherapy on systemic collagen deposition and postoperative infective complications in rectal cancer patients. Dis Colon Rectum, 2005; 48: 1573–80
22. Marijnen CA, Kapiteijn E, van de Velde CJ et al: Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: results of a multicenter randomized trial. J Clin Oncol, 2002; 20: 817–25
23. Kapiteijn E, Kranenbarg EK, Steup WH et al: Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch Colorectal Cancer Group. Eur J Surg, 1999; 165: 410–20
24. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al: Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs conventionally fractionated radiochemotherapy. Radiother Oncol, 2004; 72: 15–24
25. Bujko K, Nowacki MP, Kepka L et al: Postoperative complications in patients irradiated pre-operatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs chemoradiation. Colorectal Dis, 2005; 7: 410–6
26. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al: Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg, 2006; 93: 1215–23
27. Milsom JW, Senagore A, Walshaw RK et al: Preoperative radiation therapy produces an early and persistent reduction in colorectal anastomotic blood flow. J Surg Res, 1992; 53: 464–9
28. Jahnson S, Holtz A, Gerdin B: Anastomotic blood-flow reduction in rat small intestine with chronic radiation damage. Digestion, 1998; 59: 134–41
29. Johnson LB, Adawi D, Agren MS et al: Combination of pre-operative radiotherapy and surgery suppresses local accumulation of collagen and TGF-beta1 in rats. J Surg Res, 2006; 133: 136–42
30. Weiber S, Jiborn H, Zederfeldt B: Preoperative irradiation and colonic healing. Eur J Surg, 1994; 160: 47–51
31. Kuzu MA, Koksoy C, Akyol FH et al: Effects of preoperative fractionated irradiation on left colonic anastomoses in the rat. Dis Colon Rectum, 1998; 41: 370–76
32. Fang CB, Klug WA, Capelhuchnik P: Preoperative cobalt^{60} irradiation delays the healing of rectal anastomoses in rats. Braz J Med Biol Res, 2005; 38: 895–9
33. Kuzu MA, Koksoy C, Akyol FH et al: Colonic anastomotic healing after preoperative chemo-radiotherapy in rat. Radiat Med, 1999; 17: 181–7
34. De Meerleer G, Pattyn P, Fortan L et al: High-dose preoperative radiotherapy does not alter the strength of unilaterally irradiated colon anastomoses in rats. Int J Radiat Oncol Biol Phys, 1999; 44: 163–70
35. El-Malt M, Ceelen W, De Meerleer G et al: Influence of preoperative combined radiochemotherapy on surgical outcome and colonic anastomotic healing:

experimental study in the rat. Int J Radiat Oncol Biol Phys, 2001; 50: 1073–78

36. Ceelen W, El-Malt M, Cardon A et al: Influence of preoperative high-dose radiotherapy on postoperative outcome and colonic healing: experimental study in the rat. Dis Colon Rectum, 2001; 44: 717–21

37. Biert J, Hoogenhout J, Wobbes T, Hendriks T: High-dose preoperative irradiation without detrimental effect on early repair of anastomoses in the colon of the rat. Radiat Res, 1997; 147: 362–68

38. Biert J, Wobbes T, Hoogenhout J et al: Combined preoperative irradiation and direct postoperative 5-fluorouracil without negative effects on early anastomotic healing in the rat colon. Radiother Oncol, 1996; 41: 257–62

39. Rodel C, Sauer R: Radiotherapy and concurrent radiochemotherapy for rectal cancer. Surg Oncol, 2004; 13: 93–101