Sphincter-preserving R0 total mesorectal excision with resection of internal genitalia combined with pre- or postoperative chemoradiation for T4 rectal cancer in females

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Abstract

AIM: To evaluate the impact of chemoradiation administered pre- or postoperatively on prognosis in females following R0 extended resection with sphincter-preserving total mesorectal excision (TME) for locally advanced rectal cancer and to assess the association between chemoradiation and intra- and postoperative variables.

METHODS: Twenty-one females were treated for locally advanced but preoperatively assessed as primarily resectable rectal cancer involving reproductive organs. Anterior resection with TME and excision of internal genitalia was combined with neo- or adjuvant chemoradiation. Two-year disease-free survival analysis was performed with the Kaplan-Meier method and log-rank test. The association between chemoradiation and other variables was evaluated with the Fisher’s exact test and Mann-Whitney test.

RESULTS: Survival rate decreased in anaemic females (51.5% vs 57.4%), in patients older than 60 years (41.8% vs 66.7%) with poorly differentiated cancers (50.0% vs 55.6%) and tumors located ≤ 7 cm from the anal verge (42.9% vs 68.1%) but with the lack of importance. Patients with negative lymph nodes and women chemoradiated preoperatively had significantly favourable prognosis (85.7% vs 35.7%; P = 0.03 and 80.0% vs 27.3%; P = 0.01, respectively). Preoperative chemoradiation compared to adjuvant radiochemotherapy was not significantly associated with the duration of surgery, incidence of intraoperative bowel perforation and blood loss ≥ 1 L, rate of postoperative bladder and anorectal dysfunction, and minimal distal resection margin. It significantly influenced minimal radial margin (mean 4.2 mm vs 1.1 mm; P < 0.01).

CONCLUSION: Despite involving internal genitalia, long-term disease-free survival and sphincter preservation may be achieved with combined-modality therapy for females with T4 locally advanced rectal carcinoma. Neoadjuvant chemoradiation does not compromise functional results and may significantly improve oncological outcomes probably due to enhanced radial clearance.

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Key words: Locally advanced rectal cancer; Anterior resection; Total mesorectal excision; Hysterectomy; Chemoradiation

Szynglarewicz B, Matkowski R, Kasprzak P, Sydor D, Forgacz J, Pudelko M, Kornafel J. Sphincter-preserving R0 total mesorectal excision with resection of internal genitalia combined with pre- or postoperative chemoradiation for T4 rectal cancer in females. World J Gastroenterol 2007; 13(16): 2339-2343

http://www.wjgnet.com/1007-9327/13/2339.asp

INTRODUCTION

Since the introduction of total mesorectal excision (TME) by Heald et al[1], an optimal local control for rectal cancer and improved patient survival have been achieved comparing with traditional resection. In contrast, patients with locally advanced primarily unresectable tumors have a dismal prognosis. They require combined-modality therapy because of significant benefit from radiation, chemotherapy or both[2]. Neoadjuvant combined radiochemotherapy can increase sphincter preservation to 27%-64% and R0 resectability rate to 73%-90%,
which results in long-term disease-free survival in up to 73% patients[3,5]. For patients with locally advanced but primarily resectable rectal cancer more individual approach is postulated[6].

The aim of our study was to evaluate the impact of clinicopathological factors and chemoradiation administered pre- or postoperatively on prognosis in females following R0 extended resection with sphincter-preserving TME for primarily resectable locally advanced rectal cancer and to assess the association between chemoradiation protocol and intra- and postoperative variables.

MATERIALS AND METHODS

Patients
From January 1997 to December 2003, twenty-one female patients with histologically confirmed rectal cancer involving internal reproductive organs were operated on with curative intent (R0) and entered the study. The mean age of patients was 61.52 ± 6.49 years, median 63 (range, 47-73) years. Preoperative staging diagnosed T4 lesion infiltrating female internal genitalia in all cases. Neither involvement of other organs nor fixation to the pelvic wall was shown. Thus, tumors were assessed as locally advanced but primarily resectable. The mean tumor site was 7.90 ± 1.70 cm from the anal verge, median 7 cm (range, 5-12 cm). All females were treated with combined-modality therapy: radiation, chemotherapy and extended surgery. Table 1 summarises the main characteristics of patients, tumors and chemoradiation.

Surgery
Multivisceral excisions with curative intent were done by a multidisciplinary team of surgeons and gynaecologists. All operations were performed or closely supervised by the senior authors: the consultant of surgical oncology (J.F.) and the consultant of gynaecological oncology (Professor J.K.). All resection margins were postoperatively stated as microscopically free of cancer by pathological examination. All patients underwent anterior resection of the rectum with sphincter preservation strictly according to the total mesorectal excision method. Sharp dissection of pelvic fascia was performed carefully under direct vision down to the pelvic floor. Because of cancer involvement, the internal female reproductive organs were removed with the rectum in one tissue block. In eighteen females hysterectomy with bilateral salpingo-oophorectomy was performed. Three women underwent an additional excision of posterior vaginal wall. Straight end to end bowel reconstruction was performed using double-stapling technique. In order to prevent the anastomosis proximal diversion was used. Defunctioning transversostomy was closed after 12-24 wk.

Chemoradiation
For ten patients neoadjuvant 50.4 Gy irradiation (25 × 1.8 Gy + 5.4 Gy boost) and two five-day cycles of chemotherapy with 5-fluorouracil (325 mg/m²) and folinic acid (20 mg/m²) by intravenous bolus injection were administered, followed by surgery after 4-6 wk and postoperative four cycles of chemotherapy. In the remaining eleven females a standard adjuvant radiochemotherapy (5-fluorouracil/folinic acid- based systemic treatment in six five-day courses added to 50.4 Gy radiation) was given. Impact of chemoradiation protocol on survival and its association with intra- and postoperative variables (surgery duration, blood loss, bowel perforation, bladder disturbances, anorectal dysfunction, minimal distal and radial margin) were analysed.

Follow-up
The mean follow-up duration was 20.6 (range, 9-34) mo. It was scheduled every three months during the first postoperative year and every six months thereafter. Physical examination, blood tests, serum markers, barium enema, gynaecological examination, endoscopy, chest radiograph and abdominal ultrasound were done. In every supposition of cancer recurrence more precise investigation using endorectal sonography, CT-scanning or radioisotope imaging was performed. Besides chemoradiation impact of patient’s age, tumor site, differentiation grade, lymph node-status and presence of anaemia on survival was evaluated.

Statistical analysis
The data were analysed using software StatSoft Inc, STATISTICA for Windows ver. 5.5 A, Tulsa, OK, USA. For considered range of parameters, median and mean values with standard deviation were calculated. To examine the impact of individual factors on long-term outcome, two-year disease-free survival analysis was performed. Females not alive due to any cause and alive with any evidence of local recurrence or distant metastases were defined as not disease-free survivors. Survival was estimated by the Kaplan-Meier method. Differences between curves were analysed with log-rank test (Cox-Mantel). To compare nominal variables Fisher’s exact test was performed, for continuous variables the Mann–Withney U-test was used. Probability level of 0.05 was accepted as a significance limit.

Table 1 Baseline characteristics of patients, tumors, treatment and survival

| Parameter | n (%) | Survival rate (%) | P |
|-----------|-------|-------------------|---|
| Age ≤ 60 yr | 9 (42.8) | 66.7 | NS |
| > 60 yr | 12 (57.2) | 41.8 | |
| Tumor site > 7 cm | 15 (71.4) | 68.1 | NS |
| ≤ 7 cm | 6 (28.6) | 42.9 | |
| Differentiation grade | | | |
| Well/moderate | 12 (57.2) | 55.6 | |
| Poor | 9 (42.8) | 50.0 | |
| Anemia: absent | 18 (85.7) | 57.4 | NS |
| present | 3 (14.3) | 51.5 | |
| Lymph node-status: (-) | 7 (33.3) | 85.7 | < 0.05 |
| (+) | 14 (66.7) | 35.7 | |
| Chemoradiation | | | |
| Preoperative | 10 (47.6) | 80.0 | < 0.05 |
| Postoperative | 11 (52.4) | 27.3 | |

NS: not significant.
RESULTS

Survival analysis
There was no postoperative death. Twenty-four months after resection eleven females were still alive without any evidence of cancer recurrence, two-year disease-free survival rate was 53%. Survival was enhanced in women at the age of less than or equal to 60 years and non-anaemic patients with well or moderately differentiated tumors sited above 7 cm from the anal verge, but with a lack of importance. Significantly poorer survival was noticed in females with lymph node metastases (log-rank, \( P = 0.03038 \)) (Figure 1). Prognosis was significantly favourable for patients treated with preoperative chemoradiation (log-rank, \( P = 0.01231 \)) (Figure 2). There were seven node-positive patients in each group according to chemoradiation protocol. Survival analysis is shown in Table 2.

Chemoradiation and intra- and postoperative variables
Chemoradiation schedule did not significantly influence the volume of intraoperative blood loss, incidence of intraoperative bowel perforation, rate of postoperative bladder disturbances, incidence of postoperative anorectal dysfunction and surgery duration: mean 155 (range, 106-187) min vs mean 137 (range, 98-182) min. Postoperative chemoradiation was related to decreased minimal distal clearance: mean 9.5 (range, 9.1-33.9) mm vs mean 10.6 (range, 9.2-36.7) mm but with the lack of importance. Preoperative chemoradiation was associated with significantly enhanced minimal radial clearance: mean 4.2 (range, 3.6-7.2) mm vs mean 1.1 (range, 0.9-1.4) mm (Mann-Whitney, \( P < 0.01 \)).

DISCUSSION

Adjacent organ involvement is present in 10% rectal cancers and in 50%-57% of them fixation is caused by cancer infiltration[7,8]. For females with primarily resectable tumor involving internal genitalia the key factor to avoid oncological relapse is microscopically free R0 multivisceral excision[9,10]. Our findings are in accordance to recent studies, suggesting that aggressive approach and close surgo-c-gynaecological co-operation can provide sphincter preservation and excellent pelvic control resulting in improved long-term survival with acceptable risk of 0%-7.5% postoperative mortality and 12.5%-50.0% morbidity (mostly wound healing complications)[11-14].

Lymph node involvement is an unquestionable indicator of poor outcome. For node-positive patients five-year overall survival, two-year overall survival and disease-free survival rates are decreased to 25%, 43% and 33%, compared to 75%, 94% and 67% for patients with negative nodes, respectively[12-14]. We did not notice significant prognostic value of other clinical and pathological parameters, possibly due to the relatively small sample size. In contradiction to our results, negative predictive significance of blood loss \( \geq 1 \) L, patient’s age \( > 62-64 \) years, increased CEA serum level, poor differentiation and the presence of anaemia before treatment have been found in other studies[14-17].

The only other factor significantly related to survival in our study was chemoradiation protocol. In spite of R0 resection chemoradiation given before surgery influenced favourable prognosis with a high level of statistical importance. Due to preoperative irradiation, the complete pathological response of resectable cancer in up to 20%
patients can be achieved, tumor may downsize in 64% cases, incidence of local recurrence may be reduced to 4%, 69% patients with lymph node metastases may be rendered node-negative, and finally, overall long-term and disease-free survival rates may be enhanced to 75% and 83%, respectively [18-20]. Moreover, the addition of preoperative chemotherapy independently increases tumor response improving survival [21].

Results of comparisons of neoadjuvant therapy are discrepant. A Swedish review of over 40,000 patients reported that preoperative schedule is more effective for survival benefit [21]. In contrast, in the Uppsala trial decreased risk of local relapse was noticed for the preoperative arm but five-year survival was not significantly improved [21]. However, this study evaluated short-course hypofractionated preoperative irradiation without concurrent chemotherapy. Results from the recent controlled randomised German trial suggest that neoadjuvant radiochemotherapy is related with less toxicity, does not produce higher postoperative morbidity and is better for local control than adjuvant chemoradiation but in fact does not significantly affect overall survival [22].

The reason for the important prognostic value of the chemoradiation protocol in our study may be its association with the extent of resection margins. When feasible, striving for 2 cm distal margin is advocated because of intramural tumor spread possibility. However, it does not exceed 1 cm for 90% rectal cancers [27]. Zhao et al. [30] have reported maximum 12 mm distal intramural spread and 36 mm distal mesorectal spread. Thus, some authors claim that TME with a distal margin ≤1 cm does not seem to compromise oncological outcome, especially if resection follows combined-modality therapy [31]. In our patients, preoperative chemoradiation was not significantly related to distal margin probably due to the analysis only of the females selected for sphincter-saving resection.

Importance of circumferential clearance for rectal cancer was firstly emphasised twenty years ago by Quirke et al. [31]. Recently, during total mesorectal excision removal of radial margin at a minimum of 1 mm [31], 2 mm [31] and 3 mm [31] is postulated for adequate local control. In our series radiochemotherapy protocol was strongly associated with radial clearance and seven females not chemoradiated before surgery measured their circumferential margin ≤1 mm. The extent of resection margins for effective local control remains a matter of debate. However, our findings are supported by others, who noticed that the radial margin of ≤1 mm should be considered inadequate and positive [31]. Results of our study suggest, similarly to some others [31], that the main role of neoadjuvant combined-modality therapy for primarily resectable rectal cancer is not to enhance the distal margin but to increase the radial clearance and therefore improve local control and long-term survival.

REFERENCES

1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986; 1: 1479-1482
2. Rödel C, Sauer R. Perioperative radiotherapy and concurrent radiochemotherapy in rectal cancer. Semin Surg Oncol 2001; 20: 3-12
3. Klautek G, Feyhernd P, Ludwig K, Prall F, Foitzik T, Fietkau R, Intensified concurrent chemoradiotherapy with 5-fluorouracil and irinotecan as neoadjuvant treatment in patients with locally advanced rectal cancer. Br J Cancer 2005; 92: 1215-1220
4. Ratto C, Valentin V, Morganti AG, Barbaro B, Coco C, Sofo L, Baldacci M, Gentile PC, Poletti F, Doglietto GB, Fodoci A, Cellini N. Combined-modality therapy in locally advanced primary rectal cancer. Dis Colon Rectum 2003; 46: 59-67
5. Reerink O, Verschueren RC, Szabo BG, Hospers GA, Mulder NH. A favourable pathological stage after neoadjuvant radiochemotherapy in patients with initially irresectable rectal cancer correlates with a favourable prognosis. Eur J Cancer 2003; 39: 192-195
6. Rödel C, Sauer R. Radiotherapy and concurrent radiochemotherapy for rectal cancer. Surg Oncol 2004; 13: 93-101
7. Orkin BA, Dozois RR, Beart RW Jr, Patterson DE, Gunderson LL, Istrup DM. Extended resection for locally advanced primary adenocarcinoma of the rectum. Dis Colon Rectum 1989; 32: 286-292
8. Gall FP, Tonak J, Altendorf A. Multivisceral resections in colorectal cancer. Dis Colon Rectum 1987; 30: 337-341
9. Buhrle LM, Mensink HJ, Aalders JG, Mehta DM, Verschueren RC. Advanced rectal cancer in the female: reduction of pelvic recurrence by resection en bloc with hysterecctomy and/or posterior vaginal wall excision. Eur J Surg Oncol 1991; 17: 65-70
10. Izbicki JR, Hosch SB, Knoefel WT, Passlick B, Bloechle C, Broedtsch CE. Extended resections are beneficial for patients with locally advanced colorectal cancer. Dis Colon Rectum 1995; 38: 1251-1256
11. Aleksic M, Hennes N, Ulrich B. Surgical treatment of locally advanced rectal cancer. Options and strategies. Dig Surg 1998; 15: 342-346
12. Amshel C, Avital S, Miller A, Sands L, Marchetti F, Hellinger M. T4 rectal cancer: analysis of patient outcome after surgical excision. Am Surg 2005; 71: 901-903; discussion 904
13. Ruo L, Paty PB, Minsky BD, Wuig WD, Leshen AM, Guillem JG. Results after rectal cancer resection with in-continuity partial vaginectomy and total mesorectal excision. Dis Colon Rectum 2003; 46: 664-668
14. Lehnert T, Mehtner M, Pollok A, Schaible A, Hinz U, Herfart C. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. Ann Surg 2002; 235: 217-225
15. Szynglarewicz B, Matkowski R, Forgacz J, Pudelko M, Smorag Z, Dry J, Kornafel J. Clinical factors in prediction of prognosis after anterior resection with total mesorectal excision for carcinoma of the rectum. Oncol Rep 2007; 17: 471-475
16. Crane CH, Skibber J. Preoperative chemoradiation for locally advanced rectal cancer: rationale, technique, and results of treatment. Semin Surg Oncol 2003; 21: 265-270
17. Box B, Lindsey I, Wheeler JM, Warren BF, Cunningham C, George BD, Mortensen NJ, Jones AC. Neoadjuvant therapy for rectal cancer: improved tumor response, local recurrence, and overall survival in nonanemic patients. Dis Colon Rectum 2005; 48: 1153-1160
18. Bedrosian I, Rodriguez-Bigas MA, Feig B, Hunt KK, Ellis L, Curley SA, Vauthney JN, Delcos M, Crane C, Janjan N, Skibber JM. Predicting the node-negative mesorectum after preoperative chemoradiation for locally advanced rectal carcinoma. J Gastrointest Surg 2004; 8: 56-62; discussion 62-63
19. Crane CH, Skibber JM, Feig BW, Vauthney JN, Thomas HD, Curley SA, Rodriguez-Bigas MA, Wolff RA, Ellis LM, Delcos ME, Lin EH, Janjan NA. Response to preoperative chemoradiation increases the use of sphincter-preserving surgery in patients with locally advanced low rectal carcinoma. Cancer 2003; 97: 517-524
20. Coco C, Valentini V, Manno A, Mattana C, Verbo A, Cellini N, Gambacorta MA, Covino M, Mantini G, Micičhe F, Pedretti G, Petito L, Rizzo G, Cosimelli M, Impiombato FA, Picciochi A. Long-term results after neoadjuvant radiochemotherapy for locally advanced resectable extraperitoneal rectal cancer. Dis Colon Rectum 2006; 49: 311-318

www.wjgnet.com
21 Minsky BD, Cohen AM, Kemeny N, Enker WE, Kelsen DP, Reichman B, Saltz L, Sigurdsson ER, Frankel J. Enhancement of radiation-induced downstaging of rectal cancer by fluorouracil and high-dose leucovorin chemotherapy. _J Clin Oncol_ 1992; 10: 79-84

22 Crane CH, Skibber JM, Birnbaum EH, Feig BW, Singh AK, Delcos ME, Lin EH, Fleshman JW, Thomas HD, Kodner IJ, Lockett MA, Picus J, Phan T, Chandra A, Janjan NA, Read TE, Myerson RJ. The addition of continuous infusion 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer. _Int J Radiat Oncol Biol Phys_ 2003; 57: 84-89

23 Glimelius B, Grönberg H, Järhult J, Wallgren A, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in rectal cancer. _Acta Oncol_ 2003; 42: 476-492

24 Påhlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. _Ann Surg_ 1990; 211: 187-195

25 Sauer R, Fietkau R, Wittekind C, Rödel C, Martus P, Hohenberger W, Tschmelitsch J, Sabitzer H, Karstens JH, Becker H, Hess C, Raab R. Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. _Colorectal Dis_ 2003; 5: 406-415

26 Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R. Preoperative postoperative chemoradiotherapy for rectal cancer. _N Engl J Med_ 2004; 351: 1731-1740

27 Zhao GP, Zhou ZG, Lei WZ, Yu YY, Wang C, Wang Z, Zheng XL, Wang R. Pathological study of distal mesorectal cancer spread to determine a proper distal resection margin. _World J Gastroenterol_ 2005; 11: 319-322

28 Moore HG, Riedel E, Minsky BD, Saltz L, Paty P, Wong D, Cohen AM, Guillem JG. Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. _Ann Surg Oncol_ 2003; 10: 80-85

29 Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. _Lancet_ 1986; 2: 996-999

30 Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, Sereide O. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. _Br J Surg_ 2002; 89: 327-334

31 Nagtegaal ID, Marijnen CA, Kranenburg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. _Ann Surg Pathol_ 2002; 26: 350-357

32 Kuuvshinoff B, Maghfoor I, Miedema B, Bryer M, Westgate S, Wilkes J, Ota D. Distal margin requirements after preoperative chemoradiotherapy for distal rectal carcinomas: are &lt; or = 1 cm distal margins sufficient? _Ann Surg Oncol_ 2001; 8: 163-169

33 Wang Z, Zhou ZG, Wang C, Zhao GP, Chen YD, Gao HK, Zheng XL, Wang R, Chen DY, Liu WP. Microscopic spread of low rectal cancer in regions of mesorectum: pathologic assessment with whole-mount sections. _World J Gastroenterol_ 2004; 10: 2949-2953

34 Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrel Y, Zerbib F. Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. _Ann Surg_ 2005; 241: 465-469

_S- Editor_ Zhu LH  _L- Editor_ Wang XL  _E- Editor_ Che YB