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ORIGINAL ARTICLE

Short-course Preoperative Radiotherapy with Delayed Surgery for Locally Advanced Rectal Cancer

CL Chiang[1], FAS Lee[1], YW Wong[2], CM Poon[2], CKK Choi[1], FCS Wong[1], WK Sze[1], SY Tung[1]

[1]Department of Clinical Oncology, [2]Department of Surgery, Tuen Mun Hospital, Tuen Mun, Hong Kong

ABSTRACT

Objectives: *To review the outcome of patients with locally advanced rectal cancer who underwent short-course preoperative radiotherapy (SCPRT) with delayed total mesorectal excision.*

Methods: *Consecutive patients with locally advanced rectal cancer who underwent SCPRT with delayed surgery between January 2011 and November 2014 in Tuen Mun Hospital were retrospectively reviewed.*

Results: *Overall, 18 men and five women aged 36 to 88 years underwent SCPRT with delayed surgery owing to advanced age (n = 10), poor performance status (n = 7), and severe comorbidity (n = 6). All patients had at least one risk factor: threatened mesorectal fascia (n = 20), tumour stage 4 (n = 4), lymph node stage 2 (n = 7), and low-lying tumour (n = 5). After SCPRT, 19 of the 23 patients underwent anterior resection (n = 13) or abdominal-perianal resection (n = 6) at a median of 11 weeks and achieved R0 (n = 17) or R1 (n = 2) resection. During a median follow-up of 13 months, eight patients died due to metastasis (n = 5), medical condition without evidence of progression (n = 2), or postoperative complications (n = 1). The median survival time of the 23 patients was 34 months. The 1-year overall survival was 75.1%; the 1-year cancer-specific survival was 82.5%; and the 1-year progression-free survival was 79.3%. In 19 patients who underwent resection, six developed metastatic disease. Two patients had local recurrence who also had synchronous distant metastasis. All patients completed SCPRT without interruption. Two patients had grade 3 or above toxicity: one had perforated bowel requiring emergency operation at 3 weeks and another had grade 3 leukopenia without evidence of sepsis. In the postoperative period (≤30 days), eight patients developed surgical complications including anastomotic leakage (n = 2), septic complications (n = 3), persistent perianal infection (n = 1), and ileus (n = 2). One patient died at postoperative day 12 due to myocardial infarction. One patient developed severe late radiotherapy-related toxicity of burst stump and pelvic abscess at 5 months.*

Conclusion: *SCPRT with delayed surgery can downsize and downstage locally advanced rectal cancer and achieve a favourable toxicity profile. It is a viable option for patients who are unfit for preoperative long-course chemoradiotherapy.*

Key Words: *Margins of excision; Radiotherapy; Rectal neoplasms*

Correspondence: *Dr CL Chiang, Department of Clinical Oncology, The University of Hong Kong, 1/F, Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong.*
Email: chiangcl@hku.hk

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中文摘要

術前短期放療與延遲手術治療局部晚期直腸癌

蔣子樑、李安誠、黃耀華、潘志明、蔡國強、黃志成、施永健、董煜

目的：回顧接受短期術前放療（SCPRT）與延遲全直腸切除術的局部晚期直腸癌的患者的治療結果。

方法：回顧分析2011年1月至2014年11月間，在屯門醫院接受SCPRT與延遲手術的局部晚期直腸癌的連續患者。

結果：18例男性和5例女性年齡36至88歲，因高齡（n = 10）、一般情況差（n = 7）和嚴重合併症（n = 6）接受SCPRT與延遲手術治療局部晚期直腸癌。所有患者至少有一項危險因素：直腸內筋膜受侵（n = 20）、腫瘤4期（n = 4）、淋巴結2期（n = 7）和低位腫瘤（n = 5）。23例患者中，19例在SCPRT後中位數11週進行了前切除術（n = 13）或腹部 – 肛門切除術（n = 6），並達到R0（n = 17）或R1（n = 2）切除。在13個月的中位隨訪期間，8名患者因轉移（n = 5）、非腫瘤進展醫療情況（n = 2）或術後併發症（n = 1）而死亡。23例患者的中位生存時間為34個月。1年整體生存率為75.1%；1年癌症特異生存率為82.5%；1年無進展生存率為79.3%。在19例接受切除的患者中，6例發生轉移。兩名患者局部復發同時出現遠處轉移。所有患者不間斷地完成SCPRT。兩名患者發生3級或以上的放療毒性：一名發生腸穿孔並需要在3週時進行緊急手術，另一名發生3級白細胞減少症，但無膿毒症。在術後期間（≤30天），8例患者發生手術併發症，包括吻合口漏（n = 2）、膿毒性併發症（n = 3）、持續性肛門周圍感染（n = 1）和腸梗阻（n = 2）。一名患者術後第12天因心肌梗死死亡。一名患者5個月後出現了嚴重的晚期放療相關毒性，包括殘端破裂和盆腔膿腫。

結論：對局部晚期直腸癌患者，SCPRT與延遲手術可以縮小腫瘤並降期以及耐受性好。對於不適合長期術前放化療的患者而言，是一個可行的選擇。

INTRODUCTION

Total mesorectal excision is the standard of care for rectal cancer and has reduced the local recurrence rate to <10%.[1] For locally advanced diseases (T3/4 or N+), particularly those threatening the mesorectal fascia or adjacent organs, long-course preoperative chemoradiotherapy (LCPCRT) of 1.8-2 Gy x 25-28 fractions is often indicated to downsize or downstage the tumour and sterilise the margin for subsequent radical resection and local control.[2,3] Nonetheless, many patients are unsuitable for LCPCRT.[4]

Preoperative chemoradiation is associated with less acute toxicity and wound problems and better local control than postoperative chemoradiation.[5] Nonetheless, compared with radiation alone, chemoradiation results in more grade 3 or above toxicity and subsequent treatment interruption or discontinuation and compromised oncological outcome.[6-8]

In patients barely suitable for LCPCRT, short-course preoperative radiotherapy (SCPRT) of 5 Gy x 5 fractions, followed by immediate surgery (within 10 days) improves the local control of rectal cancer, but it is not recommended for patients with threatened resection margins as it rarely induces tumour regression.[9,10] SCPRT has been shown to induce tumour downstaging, provided that resection is delayed for at least 6 weeks after completion of SCPRT.[11-14] In the randomised Stockholm III trial, SCPRT with delayed surgery resulted in a higher pathological complete response rate than SCPRT with immediate surgery (11.8% vs. 1.7%, p=0.001).[10] SCPRT with delayed surgery achieved a radical resection rate of up to 80% to 90% in patients with advanced disease.[4,12,13] According to the European Society for Medical Oncology, SCPRT with delayed surgery is a viable option for advanced rectal cancer (threatened mesorectal fascia, T4 disease, lateral pelvic lymph node involvement), particularly in older patients or those with severe comorbidity who cannot tolerate LCPCRT.[15]

In the Hong Kong Chinese population, tolerability

and efficacy of SCPRT with delayed surgery is not well known. This study retrospectively reviewed the outcome of patients with locally advanced rectal cancer who underwent SCPRT with delayed total mesorectal excision.

METHODS

This study was approved by the ethics committee of Tuen Mun Hospital and conducted in compliance with the Declaration of Helsinki. Records of consecutive patients with locally advanced rectal cancer (low T3, T4, N2, or threatened mesorectal fascia) who underwent SCPRT with delayed surgery between January 2011 and November 2014 in Tuen Mun Hospital were retrospectively reviewed. Treatment was decided by a multidisciplinary team based on patient age, performance status (measured by the Eastern Cooperative Oncology Group score), comorbidity (measured by the Charlson Comorbidity Index), and tumour staging.

Tumour staging was determined by digital rectal examination, colonoscopy, magnetic resonance imaging (MRI) of the pelvis (for delineation of the tumour extent, relationship with mesorectal fascia and nodal status), contrast-enhanced computed tomography of the abdomen / pelvis, and radiography of the chest (for any metastasis).

Patients were simulated in the treatment position (prone with a full bladder) for treatment planning using computed tomography. The gross tumour volume was defined as the primary tumour and any significant surrounding lymphadenopathy. The clinical target volume was defined as gross tumour volume plus 2 cm margin and high-risk nodal areas of mesorectal, pre-sacral, internal iliac, and obturator lymph nodes. The planning target volume was defined as the clinical target volume plus 1 cm margin to account for setup error and organ motion. The conformal technique in 4 to 5 fields arrangement with 25 Gy in 5 fractions delivered over 1 week was used.

Patients were followed up in the last fraction and 2 and 4 weeks after SCPRT. Post-SCPRT MRI was taken at 6 to 8 weeks, and surgery was performed at 8 to 10 weeks. Patients were followed up every 3 months in the first year, and every 4 to 6 months in the second and third years.

Tumour response was determined using the Response Evaluation Criteria in Solid Tumors. Survival was calculated using the Kaplan-Meier method. Overall survival was defined as the time of commencement of SCPRT to death for any reason or the day of the last follow-up. Cancer-specific survival was defined as the time of commencement of SCPRT to death due to malignancy or the day of the last follow-up. Progression-free survival was defined as time of commencement of SCPRT to the day of metastasis or local recurrence or death from any cause, whichever occurred first.

RESULTS

Overall, 18 men and 5 women aged 36 to 88 years underwent SCPRT with delayed surgery owing to advanced age (n = 10), poor performance status (n = 7), and severe comorbidity (n = 6) [Table 1]. All patients had at least one risk factor on MRI: threatened mesorectal fascia (n = 20), tumour stage 4 (n = 4), lymph node stage 2 (n = 7), and low-lying tumour (n = 5).

Of the 23 patients, 17 were evaluated by MRI after SCPRT at a median of 8.3 (interquartile range [IQR], 7.4-10.0) weeks. Of these 17 patients, 11 had tumour response and six had static disease. Six of the 17 patients had definite downstaging of mesorectal fascia.

After SCPRT, 19 of the 23 patients underwent anterior resection (n = 13) or abdominal-perianal resection (n = 6) at a median of 11 (IQR, 9-15) weeks and achieved R0 (n = 17) or R1 (n = 2) resection. The remaining four patients did not undergo surgery owing to refusal (n = 1), deterioration of physical condition (n = 1), or distant metastasis (n = 2).

Among the 19 patients who underwent SCPRT with delayed surgery, one had pathological complete response and the remaining 18 had ypT1-2 to ypT4 disease (Table 2). In terms of overall pathological stage, two patients had ypT0-2N0 tumours, 10 had ypT3-4N0, and seven had ypT any N+. Fewer patients had lymph node involvement in the pathological specimen, compared with initial MRI assessment (36.8% vs. 70%).

During a median follow-up period of 13 (IQR, 8-23) months, eight patients died due to metastasis (n = 5), medical condition without evidence of progression (n = 2), or postoperative complications (n = 1). The median survival time of the 23 patients was 34 (95% confidence interval [CI] = 20.5-47.5) months. The 1-year overall survival was 75.1% (95% CI = 57.2%-86.4%); 1-year

Table 1. Characteristics of patients who underwent short-course preoperative radiotherapy (SCPRT) and delayed surgery for locally advanced rectal cancer (n = 23).*

Characteristic	Value
Age (years)	77 (36-88)
Sex	
Male	18 (78.3)
Female	5 (21.7)
Eastern Cooperative Oncology Group score	
1	4 (17.4)
2	11 (47.8)
3	8 (35.8)
Charlson Comorbidity Index	2 (0-5)
Indication for SCPRT with delayed surgery	
Advanced age	10 (43.5)
Poor performance status	7 (30.4)
Severe comorbidity	6 (26.1)
Tumour position (from anal verge)	
Low (0-5 cm)	5 (21.7)
Mid-upper (>5 cm)	18 (78.3)
Tumour stage	
T3	19 (82.6)
T4	4 (17.4)
Lymph node stage	
N0	7 (30.4)
N1	9 (39.1)
N2	7 (30.4)
Mesorectal fascia status	
>1 mm	3 (13.0)
Involved or threatened (≤1 mm)	20 (87.0)

* Data are presented as median (range) or no. (%) of patients.

Table 2. Pathological outcome in patients undergoing curative resection (n = 19).

Outcome	No. (%) of patients
Tumour stage	
Pathological complete response	1 (5.3)
ypT1-2	1 (5.3)
ypT3	15 (78.9)
ypT4	2 (10.5)
Nodal stage	
ypN0	12 (63.2)
ypN+	7 (36.8)
Overall stage	
Stage I: ypT0-2N0	2 (10.5)
Stage II: ypT3-4N0	10 (52.7)
Stage III: ypT any N+	7 (36.8)
Resection margin status	
>1 mm (R0)	17 (89.5)
≤1 mm (R1)	2 (10.5)

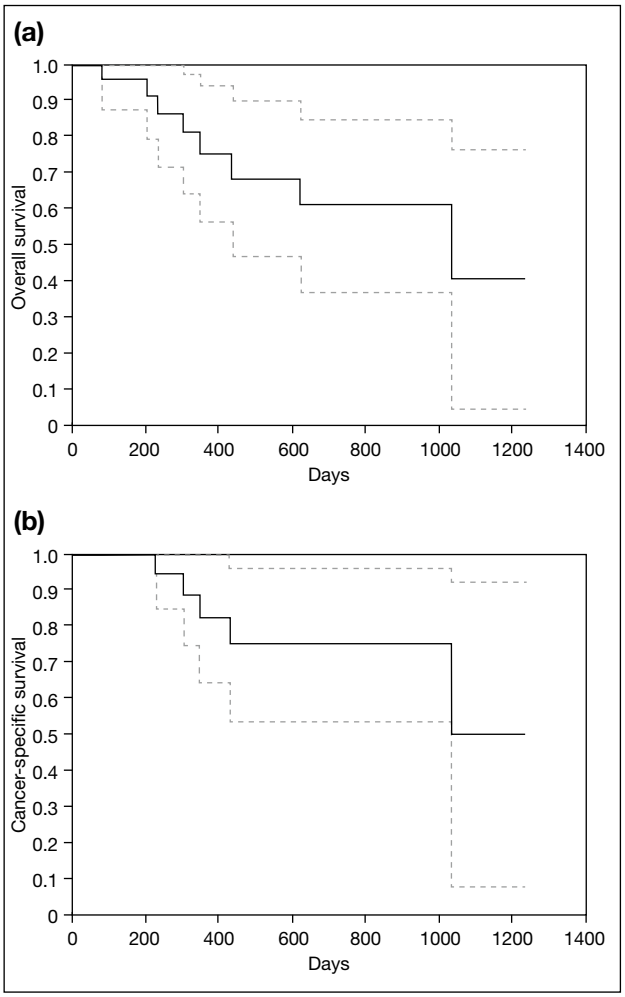

Figure. (a) Overall survival and (b) cancer-specific survival of patients with short-course preoperative radiotherapy and delayed surgery.

cancer-specific survival was 82.5% (95% CI = 61%-92.8%); and 1-year progression-free survival was 79.3% (95% CI = 55.6%-91.3%) [Figure]. In 19 patients who underwent resection, six developed metastatic disease, with the first site at the lung (n = 2), liver (n = 1), peritoneum (n = 1), and multiple sites (n = 2). Two patients had local recurrence and also synchronous distant metastasis; they had partial response and margin-negative resection. In one patient, the resection was an intra-mesorectal plane excision that may have accounted for an increased risk of local recurrence, as total mesorectal excision is an independent predictor of local control. In the other patient, the local mass was more likely to have been a component of widespread dissemination due to the aggressive biology of the tumour, rather than a failure of local treatment.

All patients completed SCPRT without interruption. In the early post-SCPRT period (<90 days), two patients had grade 3 or above toxicity: one had perforated bowel requiring emergency operation at 3 weeks (grade 4 toxicity) and another had grade 3 leukopenia without

evidence of sepsis. The most common grade 2 or above toxicities were: proctitis (n = 6), diarrhoea (n = 3), anaemia (n = 4), and fatigue (n = 2). In the postoperative period (≤30 days), eight patients developed surgical complications including anastomotic leakage (n = 2) [one of them required re-operation], septic complications (n = 3), persistent perianal infection (n = 1), and ileus (n = 2). One patient died at postoperative day 12 due to myocardial infarction. One patient developed severe late radiotherapy-related toxicity (≥90 days) of burst stump and pelvic abscess at 5 months.

DISCUSSION

SCPRT with delayed surgery for patients with advanced rectal cancer who are unsuitable for chemotherapy has shown promising outcome.[4,12,13] Of the patients who underwent surgery, 85% to 91% achieved a negative-margin resection, with a local recurrence rate of 0% to 12.5%.[4,12,13] The pathological complete response rate after SCPRT with delayed surgery without consolidation chemotherapy is usually 10% (range, 1-12%).[4,12-14,16,17]

The side-effect profile of SCPRT with delayed surgery is more favourable than that of LCPCRT. In a phase 2 trial of 89 patients with stage 1-3 rectal cancer, SCPRT with delayed surgery was associated with less acute overall toxicity (27% vs. 64%, p = 0.001) and grade 3 or above toxicity (8% vs. 2%), with a comparable postoperative complication rate to LCPCRT.[8] SCPRT with delayed surgery is well-tolerated, with the rate of grade 3 or above toxicity being 2% to 5% and the rate of postoperative complications being 30% to 50%, with 10% being severe (such as death or requiring re-operation).[3,11,14-18]

The clinical outcome and toxicity profile of SCPRT with delayed surgery in our patients are comparable to those reported in other studies.[4,11-14,16,17] All our patients had locally advanced disease and thus upfront surgery was inappropriate, as it may have resulted in R1-2 resection that is unsalvageable by postoperative irradiation, as well as inferior local control and survival.[19,20] SCPRT with delayed surgery can induce tumour regression and downstaging to enable subsequent radical resection.

Nonetheless, routine use of SCPRT in fit patients is not supported; LCPCRT remains the standard of care and achieves a pathological complete response rate of 9% to 14%.[5,21,22] In a study of 98 patients, LCPCRT was superior to SCPRT in the rates of pathological complete response (13% vs. 3%) and downstaging of tumour to stage 0-1 (39.1% vs. 21.6%), although the two regimens were comparable in the rates of negative-margin resection and sphincter preservation.[23]

Distant metastasis was the main cause of failure (n=6) in our patients. Whether adjuvant chemotherapy would improve survival in rectal cancer patients after neo-adjuvant radiotherapy is controversial.[24] Nonetheless, our patients were unlikely to be fit for systemic chemotherapy.

In our patients, the median interval from completion of SCPRT to resection was 11 weeks, which was longer than the 7 to 8 weeks reported in other studies.[4,11-14,16,17] According to our hospital practice, a longer waiting interval may lead to a better response. In a meta-analysis, longer waiting interval (more than 6 to 8 weeks) after LCPCRT increases the pathological complete response rate without compromising the oncological outcome.[25] Nonetheless, two of our patients developed distant metastasis during the waiting interval; the metastasis rate of 12% is similar to that reported in one study.[4]

Our study had several limitations. The sample size was small and from a single hospital. The study was retrospective and had intrinsic bias; the institutional protocol was not robust enough to detect the whole spectrum of toxicities. The follow-up period was short and late complications were not accounted for. The Stockholm III trial is expected to provide more data regarding the long-term oncological outcome and late toxicity of SCPRT with delayed surgery. Nonetheless, our sample was homogeneous; only those who were unfit for LCPCRT were included.

CONCLUSION

SCPRT with delayed surgery can downsize and downstage the locally advanced rectal cancer and achieve a favourable toxicity profile. It is a viable option for patients who are unsuitable for LCPCRT.

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