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Scientific Article

Radiation Therapy Dose Escalation to Clinically Involved Pelvic Sidewall Lymph Nodes in Locally Advanced Rectal Cancer

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Abstract

Purpose: Lateral pelvic sidewall lymph nodes (PSW LN) may be involved in up to 24% of locoregionally advanced rectal cancers. PSW LN are not resected in total mesorectal excision (TME), and no standard of care regarding the management of PSW LN exists in the United States. We assessed our institutional experience of preoperative radiation therapy (RT) boost to clinically involved PSW LN that were not planned for resection.

Methods and materials: Data from all patients with rectal adenocarcinoma treated between 2006 and 2018 were reviewed to identify those who received a cumulative dose of >50.4 Gy to suspicious PSW LN during neoadjuvant chemoradiation therapy (nCRT). Demographic, cancer characteristic, treatment, and toxicity data were derived from the chart.

Results: Of a total of 261 patients, 12 patients met the inclusion criteria. The median age was 47.5 years, and 83% of patients were men. All patients had T3/4 disease, 17% of patients had N1b disease and the remainder had N2 disease, and 33% had M1 disease (all ≤2 metastases). Seventy-five percent of patients had moderately or poorly differentiated histology. The mean distance from the anal verge was 4.85 cm (range, 2-8.9 cm), and 58% had ≥2 PSW LN with an average short axis diameter of 1.11 cm (range, 0.4-3.2 cm). Boost doses ranged from 53.48 Gy to 60.2 Gy in 27 to 30 fractions (1.8-2.15 Gy/fraction). The median follow-up time was 18 months. One patient who received concurrent capecitabine and irinotecan had grade 3 perineal dermatitis and anemia during nCRT. The median hospitalization time for TME was 6.5 days. Within 90 days of TME, 1 patient required surgical exploration for perineal wound breakdown, and another required a blood

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transfusion for anemia. At the time of the last follow up, 75% of patients were alive. Local control at 12 months was 90%.

Conclusions: RT dose escalation to nonresected PSW LN during nCRT was well tolerated with a low risk of acute toxicity and perioperative complications and has a high rate of local control at 12 months. RT boost warrants further study in patients with clinically involved nonresected PSW LN.

Introduction

Colorectal cancer is the third most common cancer in the United States[1] with approximately 40,000 new cases annually. A large surgical series suggested that the prevalence of pelvic sidewall lymph node involvement (PSW LNI) is approximately 15% and may be up to 24% in patients with positive perirectal lymph nodes.[2,3] PSW LNI is associated with a higher risk of locoregional recurrence and poorer overall survival.[2] The current standard of surgical care in North America and Europe is total mesorectal excision (TME). However, PSW LN are not routinely resected with TME and represent an important potential source of locoregional failure.

Lateral pelvic lymph node dissection (LLND) with TME is the standard of care in Japan.[4] However, owing to increased morbidity with LLND observed in early studies, poorer prognosis associated with PSW LNI, and a previous lack of randomized data demonstrating a benefit to extended surgery, LLND was largely abandoned in the West.[5] A Japanese phase 3 trial showed that TME was not noninferior to TME + LLND.[6] However, patients who underwent TME + LLND had a significantly increased operation time, blood loss, and trend toward increased grade 3 to 4 adverse events.[7] Neoadjuvant chemoradiation therapy (nCRT) followed by TME remains the accepted standard therapy for stage II to III rectal adenocarcinomas in North America and Europe.[8–11]

At the present time, there is no accepted standard of care to manage clinically involved PSW LN, and most patients in the West receive nCRT and TME without LLND. An alternative option to intensify local therapy without extending surgical resection margins is increasing the radiation dose to clinically involved or at-risk nodes during nCRT. However, the safety of radiation therapy (RT) boost needs to be established, and no published patient data exist on RT boost safety or efficacy to PSW LN in patients with rectal cancer.

Herein, we assess our institutional experience with preoperative RT boost (sequential or simultaneously integrated) to clinically involved PSW LN that were not planned to undergo resection.

Methods and Materials

Data from all patients with International Classification of Diseases 9 or 10 diagnosis codes for rectal cancer who were treated at our RT department between 2006 and 2018 were reviewed, including patients who had biopsy-proven rectal adenocarcinoma and received a RT boost to a cumulative dose of $>$50.4 Gy to clinically suspicious PSW LN during nCRT. Clinical suspicion was primarily based on lymph node size (short axis $>$0.5 cm) but ultimately determined by a multidisciplinary tumor board. Patient charts that met these criteria were further reviewed for demographic, cancer characteristic, treatment, and toxicity (severity retrospectively graded per the Common Terminology Criteria for Adverse Events, version 4.0) data. Patients whose PSW LN received a cumulative dose of $\leq$50.4 Gy, short-course nCRT, or whose histology was something other than adenocarcinoma were excluded. PSW LN included lymph nodes in the following areas: obturator, sidewall, internal or external iliac region, and common iliac region. Dosimetry data was obtained from treatment planning and oncology information systems. No predefined protocol for RT boost target volume delineation existed.

The primary endpoint was to retrospectively determine the rate of grade 3 to 4 adverse events during neoadjuvant therapy. Adverse events during neoadjuvant therapy were determined by reviewing all available radiation and medical oncology notes. Intraoperative events were determined by reading all operative notes. Immediate postoperative complications were assessed by reviewing all hospital discharge notes. Postoperative adverse events were determined by a review of all available medical notes. Charts were evaluated to determine if any unplanned hospital admissions occurred, in which case admission and discharge notes were reviewed to evaluate whether the admission was related to complications of treatment. Each chart was reviewed through to the most recent follow up to detect documentation of adverse events. Survival, control, and follow-up rates were calculated from the date of the

Table 1 Patient demographics, treatment course

Case no.	Age at Dx	Sex	Race	ECOG PS	cT	cN	cM	No. PSW LNI	Least dimension PSW LN (cm)	Greatest dimension PSW LN (cm)	Neo-adjuvant chemo	No. cycles	Total Dose (cGy)
1	32	M	Asian	0	T3	N2b	M0	3+	1.3		FOLFOX*	8*	6020
2	50	M	White	1	T4b	N2NOS	M1a	1	1	1	FOLFOX	12	6020
3	57	M	Asian	0	T4b	N1b	M0	3+	0.8	1.4			6020
4	45	M	Latino	0	T3	N1b	M1b	2	0.9	1.6	FOLFOX	4	5600
5	34	M	White	0	T4a	N2NOS	M1a	2	0.6	0.9	FOLFOX	5	5600
6	53	M	White	0	T3	N2b	M0	3+	0.4	0.8			5460
7	35	F	White	0	T3	N2a	M0	1	3.2	3.7			5404
8	76	M	White	1	T3	N2a	M0	1	1.3	1.4			5400
9	38	M	White	0	T3	N2a	M0	1	0.8				5400
10	43	F	White	1	T4	N2	M0	2	1	1.4	Other†	†	5400
11	60	M	White	0	T3	N2a	M0	1	0.6	0.7			5400
12	56	M	White	1	T3	N2a	M1a	2	1.4	2	FOLFOX	11	5348

Abbreviations: ECOG PS = Eastern Collaborative Oncology Group performance status; FOLFOX = leucovorin, 5-fluorouracil, and oxaliplatin; LN = lymph node; LNI = lymph node involvement; nCRT = neoadjuvant chemoradiation therapy; PLND = pelvic lymph node dissection; PSW = pelvic side wall.

* This patient received nCRT first, followed by consolidative neoadjuvant FOLFOX. The other patients were administered induction systemic therapy, followed by nCRT before surgery.

† Complex regimen at an outside institution included capecitabine, erlotinib, bevacizumab, and naturopathic supplements, then capecitabine with oxaliplatin + bevacizumab, then cetuximab, before starting nCRT with concurrent capecitabine with irinotecan. The exact number of cycles of induction therapy could not be determined.

diagnostic biopsy. Local control was defined as no evidence of growth of the lymph node(s) treated with an RT boost on imaging. Locoregional control was defined as no evidence of new pelvic disease or progression in size of treated unresected pelvic disease on imaging. This study was approved by our institutional review board (IRB ID: STUDY00003900).

Results

Between 2006 and 2018, a total of 261 patients with rectal cancer of all stages were treated, 12 of whom received a RT boost of >50.4 Gy during nCRT for clinically involved PSW LN. Patient demographics and treatment course information are summarized for each patient in Tables 1 and 2. Ten patients were men (83%), and the median age was 47.5 years (range, 32-76 years). Two-thirds of patients had clinical T3 disease, and the remaining patients had T4 disease. Two patients (17%) had cN1b lymph node involvement, and 10 patients (83%) had N2 disease. One-third of patients had distant metastatic disease (M1) with ≤2 metastases. Two patients had well differentiated adenocarcinoma (17%), but most had moderately or poorly differentiated malignancy (50% and 25%, respectively), and 1 patient's pathology test results did not include tumor grade. Three patients (25%) had ≥3 clinically involved PSW LN, and the remainder of patients had <3. The mean PSW LN short axis was 1.11 cm (range, 0.4-3.2 cm). The lymph nodes of 1 patient with a short axis of <0.5 cm were clinically suspected by the tumor board based on radiographic morphology and the number of lymph nodes. The average PSW LN long axis was 1.49 cm (range, 0.7-3.7 cm). The mean distance of the rectal primaries from the anal verge was 4.85 cm (range, 2-8.9 cm).

Neoadjuvant therapy for each patient is summarized in Table 1. Five patients (42%) received induction chemotherapy before starting nCRT. Another patient received consolidative systemic therapy after nCRT before his surgery. Most patients received 5-fluorouracil/oxaliplatin-based systemic therapy. The average number of completed neoadjuvant cycles was 8 (range, 4-12 completed cycles). All patients received concurrent capecitabine with RT. One patient received capecitabine and irinotecan during nCRT. Two patients (17%) received sequential boosts at 1.8 Gy per fraction, and the other patients were treated with a simultaneous, integrated, boost technique using intensity modulated RT (IMRT) with fractional doses >1.8 Gy (range, 1.91-2.15 Gy/fraction). These doses were selected on the basis of the clinical judgment of the treating radiation oncologist, and often, the limiting factors were proximity to the bowel and overall size of the boost volume with typically lower doses per fraction used for larger boost volumes.

Representative images from a patient planned with a simultaneous integrated boost to 60.2 Gy are shown in the Figure 1. Seven patients (58%) were treated to a cumulative dose of >54 Gy, and 25% of patients received 60.2 Gy in 28 fractions. Table 3 lists pertinent dose-volume histogram data for key organs at risk. Generally, the small bowel dose was kept acceptably low with

Table 2 Surgical and adjuvant therapy characteristics

Case No.	Days from neoadjuvant therapy to surgery	Surgery details	IORT (cGy)	Days from surgery to discharge	Adjuvant chemotherapy	No. cycles
1	15	Total proctocolectomy	1000	12		
2	No surgery	No surgery			CAPIRI + Bev*	11*
3	66	LAR, robot-assisted		26	FOLFOX	12
4	58	APR, robot-assisted		3		
5	35	LAR, laparoscopic		6	FOLFOX	6
6	Lost to follow-up	Lost to follow-up				
7	58	APR, robot-assisted	1000	5	FOLFOX	7
8	98	APR, robot-assisted		7		
9	105	LAR, robot-assisted		12	CAPOX	5
10	36	TPE, posterior vaginectomy, PLND		10	CAPIRI	8
11	62	APR, robot-assisted		4	FOLFOX	8
12	56	LAR		3	Capecitabine	4

Abbreviations: APR = abdominoperineal resection; Bev = bevacizumab; CAPIRI = capecitabine + irinotecan; cM = clinical metastasis classification; FOLFOX = leucovorin, 5-fluorouracil, and oxaliplatin; IORT = intraoperative radiation therapy; LAR = low anterior resection; PLND = pelvic lymph node dissection; TPE = total pelvic exenteration.

* Patient had progression of extra-pelvic disease, and subsequently received multiple lines of palliative chemotherapy after CAPIRI with bevacizumab.

low percent volumes at 50 Gy and 45 Gy, and the absolute volumes of the small bowel at these doses were low in all patients for whom there was information available. The bladder and femoral head doses were low (Table 3). Table 4 outlines the target volume doses. The average planning target volume (PTV) was 217.6 cc (range, 27.8-865.1 cc). Tables 3 and 4 show that ample PTV coverage for the RT boost targets was achieved in all patients. RT boost target volumes were variably defined with 1 of 2 methods typically used: clinical target volume consisting of the extra-mesorectal lymph node region that contains the clinically involved lymph node contoured with a 5 to 7 mm margin from clinical target volume to PTV or gross tumor volume of individual extra-mesorectal lymph nodes contoured with a 7 to 10 mm margin from the gross tumor volume directly to the PTV. Table 5 outlines the dose constraints for contoured volumes, including the small bowel. Two plans used the term "bowel", and were reviewed including both the small and large bowels. Dose constraints were available for all patients except patient 10. The sacral plexus was not contoured.

Table 6 summarizes the toxicity experienced during treatment for patients who received ≥14 fractions of nCRT. Patient 6 transferred care to another institution after 13 fractions, and outside treatment records were not available for review. The patient's death date was obtained from public records. The majority of patients tolerated treatment well. One patient (8%) received capecitabine + irinotecan-based nCRT and experienced grade 3 dermatitis and anemia, which required a blood transfusion. The maximum treatment break during nCRT was 3 days.

Of the 12 patients who received ≥14 fractions, 1 patient transferred care and was lost to follow up, and 1 patient developed distant progression of disease and did not undergo a resection. For the 10 patients who received TME, the median time from whichever the neoadjuvant therapy last preceded surgery (nCRT or consolidative chemotherapy) was 58 days (range, 15-105 days). One

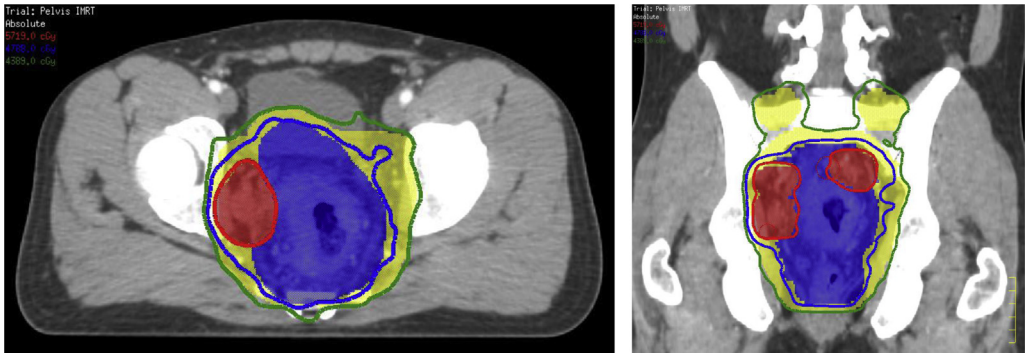

Figure 1 Representative images from radiation therapy boost plan for case number 1 (axial and coronal views).

Table 3 Organ at risk dose-volume histogram and PTV boost coverage data

Case No.	Rectum	Small bowel				Bladder			Femoral heads		PTV boost	
	Max point (cGy)	√50 (%)	V45 (%)	V45 (cc)	Max point (cGy)	√45 (%)	V30 (%)	Max point (cGy)	√45 (%)	Max point (cGy)	D98%	D95%
1	6018	0	5	29	5109	23	96	5469	0	4096	90	100
2	6027	0	16	57	5141	32	98	5750	0	4234	99	100
3	5535	0	5	26	5002	25	72	5525	0	4781	90.4	99
4	N/a	0	4	16	5051	13	46	5419	0	4087	99	100
5	5864	0	7	18	5150	36	93	5520	0	4502	100	100
6	5855	5	9	63	5638	44	79	5350	0	4164	100	100
7	5767	3	22	30	5369	20	76	5675	10	5196	95	100
8	5670	0	0	0	4775	35	57	5691	0	4639	100	100
9	5445	15	20	113	5556	21	57	5225	0	3707	99	100
10*	5768				5839			5992		5812		
11	5492	0	2	8	5170	23	49	5482	0	4119	100	100
12	N/a	0	16	16	4795	31	80	5658	0	4022	100	100

Abbreviations: max = maximum; N/A = not applicable; PTV = planning target volume.
The maximum point dose is a pixel dose. Not applicable means this structure was not contoured.

* Unable to retrieve patient's plan in the treatment planning system, and the maximum point doses were found on plan print-outs in the oncology information system. Of note, this patient's small bowel dose point is from a contour that included both the large and small bowels as a single bowel contour volume.

patient had a combined operation with gynecologic oncologists who performed PSW LN dissection in addition to the TME performed by the patient's colorectal surgeon and was found to be ypN0. Eight of 10 patients who underwent TME were ypN0.

Two patients received intraoperative RT (IORT) boosts of 10 Gy electrons to either the anticipated close margins or unresectable lymph node areas. Patient 1 developed a presacral abscess during admission for surgery 7 days after surgery. The IORT boost was to the anterior pelvic wall margin. One patient was discovered during surgery to have an asymptomatic deep vein thrombosis, but otherwise no intraoperative complications were reported. Immediate postoperative complications (ie, before discharge from admission for surgery) were seen in 5 patients: Pre-sacral abscess, small bowel obstruction managed without surgery, bilateral lower extremity sensory neuropathy, ischemic colostomy that requires revision, and postoperative ileus with prolonged nasogastric tube use. The median number of days from surgery to discharge was 6.5 (range, 3-26 days). Within 90 days of surgery, 2 patients had complications, with 1 patient who had perineal wound breakdown that required a surgical revision in the setting of chronic steroid therapy and another patient who had symptomatic anemia that was managed with an outpatient transfusion. The same patient with chronic steroid therapy who had a perineal wound breakdown within 90 days also had a challenging body habitus that required the presence of 2 attending surgeons at the time of the resection. The patient underwent several

Table 4 Target volumes and doses

Case no.	Cumulative total dose (cGy)	Planned fractions	GTV rectal volume (cc)	GTV LN volume (cc)	PTV boost volume (cc)	Minimum dose to PTV boost (cGy)	Max dose to PTV boost (cGy)	Mean dose to PTV boost (cGy)
1	6020	28	153.8	16.7	92.2	5637	6453	6097
2	6020	28	61.7	4.5	27.8	5812	6197	6081
3	6020	28	137.2	3.1	55.3	5474	6287	6056
4	5600	28	271.3	11	33	5338	5922	5744
5	5600	28	79.3	4.3	87.2	5496	6000	5710
6	5460	28	124.5	6	274	5450	5855	5648
7	5404	28	49.3	0.6	745.7	4950	5885	5495
8	5400	30	71.7	8	865.1	4870	5785	5571
9	5400	27	94.3	2.9	76.6	5178	5810	5480
10	5400	30	145.7	6.4	NR	2097	6140	5587
11	5400	27	50.4	1.4	32.4	5432	5649	5535
12	5348	28	50.3	4.2	104.6	5217	5725	5513

Abbreviations: GTV = gross target volume; LN = lymph node; NR = not reported; PTV = planning target volume.

Table 5 Small bowel dose constraints

Volume name	Max dose	Relative volume constraint			Absolute volume constraint			Patients treated with constraints
		Dose	Limit	Volume (%)	Dose	Limit	Volume (cc)	
Small bowel	5150							1, 2, 3, 8
	5300							6
	5400							7, 11
		4000	≤	40				6
		4000	<	25				11
		4500	<	25				6
		5000	<	10				11
					1500	<	120	9
					3500	<	150	3, 7, 8, 11
					4000	<	150	1, 2, 7
					4000	<	70	3, 7, 8
					4500	<	195	9
					4500	<	100	1, 2, 3, 5
					4500	<	90	7
					4500	<	35	3, 7, 8
					5000	<	10	5
					5040	<	10	7
Bowel*	5150							4, 12
					2500	<	185	4
					3000	<	155	4
					3500	<	40	4
					3500	<	150	12
					4000	<	70	12
					4000	<	30	4
					4500	<	35	12

Dose is in units of cGy. No organ at risk constraint documentation could be found for patient 10.
* Volume included both the small and large bowels.

subsequent admissions >90 days after surgery for recurrent wound infections and ultimately died of sepsis from a pelvic abscess 16 months after surgery. The patient received a sequential RT boost to a total dose of 54 Gy.

After TME, 7 of 10 resected patients received adjuvant systemic therapy (Table 2). The average number of completed adjuvant cycles was 6.4 (range, 3-12 completed cycles). One patient underwent a metastasectomy for 2 pulmonary metastases. The median follow-up time was 18 months (range, 5-63 months). Median overall survival was not yet reached, but 9 patients (75%) were alive at the time of the last follow up, including 2 patients who were alive with the disease. The 1-year overall survival rate was 91.7%, and the median locoregional progression-free survival (ie, any progression in the pelvis) was 16 months (range, 8-22 months). After excluding 1 patient who transferred care after 13 fractions and another patient who received a PSW LN dissection along with the TME, local control of PSW LN at 12 months was 90% and locoregional control was 80%.

One patient had progression of disease in an unresected PSW LN that received an RT boost, and another patient had a locoregional recurrence in a new PSW LN contralateral to the originally clinically involved and RT boosted PSW LN (boosted LN remained controlled).

Discussion

Our case series of 12 patients with locally advanced rectal adenocarcinoma with clinically involved PSW LN who were not planned to undergo LLND suggests that RT boosts >50.4 Gy and up to 60.2 Gy in 28 fractions, using daily doses up to 2.15 Gy per fraction, are well tolerated during neoadjuvant therapy and associated with high rates of short-term local control and no detected increased risk of intraoperative complications. To the best of our knowledge, this is the first report of various radiation dose-escalation schemes in patients with clinically involved PSW LN and suggests that further research into the safety and efficacy of RT boost for PSW LN involvement is merited.

PSW LN are an important contributor to locoregional failure and death in patients with rectal cancer.[2,12,13] One approach to mitigate the risks associated with PSW LNI includes extending the surgical margins to include the pelvic sidewall. LLND has been largely abandoned by Western colorectal surgeons,[5,14] but widely adopted and undergone considerable refinement in Japan and Korea, including the development of nerve-sparing techniques[15] and robotic surgery.[16] In 2017, Fujita et al[6] published the results of the Japan Clinical Oncology Group trial

Table 6 Adverse events of patients completing ≥14 fractions of RT boost

Case no.	Pre-nCRT chemotherapy		nCRT with RT boost			Post-nCRT preoperative chemotherapy	Intraoperative, immediate postoperative, and 90-day surgical complications			
	Grade	Details	RT break (days)	Grade	Details	Adverse events	Intra operative	Immediate postoperative	Surgery to discharge (days)	90 day
1			1	1	Anoproctitis	No	No	Pre-sacral abscess	12	Symptomatic anemia, out-patient transfusion
2	3;3	Neuropathy; mucositis	0	1	Hand foot syndrome	–	–	–	–	–
3			3	2	Allergic reaction to capecitabine	–	No	SBO managed non-operatively	26	No
4			1	1	Diarrhea	–	No	No	3	No
5			3	1	Diarrhea	–	No	Bilateral lower extremity sensory neuropathy	6	No
7			3	1	Anoproctitis	–	No	No	5	No
8			0	1	Anoproctitis	–	No	Ischemic colostomy requiring revision	7	Perineal wound breakdown requiring surgery
9			0	1	Anoproctitis	–	No	Postop ileus with prolonged NGT use	12	No
10		Disease progression	0	3;3	Perineal dermatitis; anemia	–	DVT found intra-op	No	10	No
11			2	1	Anoproctitis	–	No	No	4	No
12	3	Hand foot syndrome	1	2	Hand foot syndrome	–	No	No	3	No

Abbreviations: DVT = deep vein thrombosis; nCRT = neoadjuvant chemoradiation therapy; NGT = nasogastric tube; RT = radiation therapy; SBO = small bowel obstruction.
"Immediate postoperative" is defined as the time from surgery to hospital discharge.
– indicates not applicable (ie, patient did not have post-nCRT pre-operative chemotherapy, surgery, etc.)

0212, a large, prospective, randomized trial of 701 patients with stage 2-3 rectal cancer with PSW LN measuring ≤1 cm who were randomized to TME + LLND versus TME alone cohorts. The 5-year relapse-free survival rates were 73.4% versus 73.3%, respectively, with a hazard ratio (HR) of 1.07 (90.9% confidence interval [CI], 0.84-1.36). Despite the extraordinary numerical similarity, this study did not find TME to be noninferior to TME + LLND (*P*-value for noninferiority = .0547), and supported TME + LLND as standard of care in Japan. The 5-year overall survival rate was also similar between TME + LLND and TME at 92.6% versus 90.2%, respectively (HR: 1.25; 95% CI, 0.85-1.84). A significant difference was observed in local recurrence, favoring TME + LLND (7% vs 13%; $P = .02$). No neoadjuvant radiation or chemoradiation was used, and adjuvant RT was rarely used.

Although TME + LLND appears to be effective and its technique much improved, concerns about intraoperative complications and adverse events remain. Patients who underwent TME + LLND versus TME had significantly longer operative times (360 vs 254 minutes; $P < .0001$) and blood loss (576 vs 337 ml; $P < .0001$).[7] There was a nonsignificant trend toward higher grade 3-4 complications with TME + LLND (22% vs 16%; $P = .07$).[7] These concerns, combined with local control benefits observed in trials that incorporate neoadjuvant therapy, have driven interest to explore the efficacy of neoadjuvant therapy and address suspected PSW LNI.

No prospective randomized trials have compared nCRT + TME with TME + LLND. A matched analysis[17] of patients who were randomized in a Dutch rectal trial[9] between TME and short-course RT followed by TME (RT + TME) compared with the Tokyo National Cancer Center Hospital database of patients treated with LLND found similar rates of local recurrence between RT + TME versus LLND (5.8% vs 6.9%; HR: 1.0; 95% CI, 0.6-1.8), which suggests that preoperative RT may be able to successfully treat PSW LNI. nCRT has become an accepted part in the management of stage II-III rectal cancers, and several retrospective reports have been published exploring its incorporation into treatment paradigms with or without LLND.[18–20] All studies used standard nCRT to 45 Gy with rectal primary 5.4 Gy boosts. These papers found locoregional failure rates of 8% to 12%, of which 40% to 83% were PSW LN recurrences. Recently Ogura et al[21] published the results of a large international retrospective study of >1200 patients with clinical T3-4 low rectal primaries who underwent surgery. A 19.5% rate of lateral lymph node recurrence at 5 years after surgery was observed in patients with pelvic sidewall lymph nodes of a ≥0.7 cm short axis diameter who underwent nCRT (both short and long course were included) followed by TME. These combined findings demonstrate that pelvic sidewall failure remains a clinically important concern in the nCRT era.

A key question is whether intensifying RT to enlarged PSW LN during nCRT can supplant LLND. If so, which is less toxic, intensified neoadjuvant therapy or extended surgical resection? Other studies investigated various combinations of systemic-dosed chemotherapy, chemoradiotherapy, and TME for stage II-III rectal cancers and demonstrated variable rates of complete pathologic response. One study suggested a pathologic complete response rate as high as 27%, with 47% of all patients studied achieving >90% pathologic response.[22] These results suggest that RT may provide adequate local control for some patients, but a question remains whether RT dose intensification would improve pathologic response rates. Our case series is too small and the follow-up time too short to accurately characterize local and locoregional control rates.

Whether RT boosts increase the risk of immediate and delayed postoperative complications remains unclear. One patient (patient 8) experienced significant wound complications, including an ischemic colostomy site that required colostomy revision in the immediate postoperative setting and multiple episodes of wound breakdown and abscess formation. The patient ultimately died of sepsis from a perineal abscess 16 months after surgery. This patient had the largest PTV boost volume (865.1 cc), which included the entire mesorectum and right obturator lymph node bed. Of note, this patient was treated with a sequential IMRT-based boost to one of the lowest overall doses in the series (54 Gy in 30 fractions at 1.8 Gy/fraction). Perhaps a dose-volume interaction with toxicity was responsible for increased late toxicity; however, the next largest PTV boost volume was 745.7 cc in patient 7, who was treated to a cumulative dose of 54.04 Gy in 28 fractions at 1.93 Gy per fraction using a simultaneous integrated boost with IMRT. This patient did not have any grade 2+ early or late adverse effects from treatment. Neither patient 7 or 8 had neoadjuvant systemic therapy. Patient 7 had higher doses to all organs at risk compared with patient 8 (Table 3) and received a 10 Gy intraoperative electron boost and 7 cycles of adjuvant FOLFOX. Patient 8 received no additional therapy, except for nCRT and TME. Patient 8 may have had other health factors placing him at a greater risk for wound complications, including chronic systemic steroid therapy. Indeed, other comorbidities, including body habitus and anatomy, necessitated the presence of 2 experienced attending colorectal surgeons for the TME.

Another patient (patient 1) developed a presacral abscess 7 days after resection, which required a drain for source control. The patient was ultimately discharged 12 days after surgery and received an IORT boost to the anterior pelvic wall for a close margin. The other patient who received an IORT boost did not have any postoperative complications. Too few patients received IORT to determine how much contributed to toxicity. However, the presacral abscess may be considered a potential immediate postoperative complication of RT.

This case series is subject to the shortcomings of retrospective data. Adverse events and their severity were abstracted from available documentation, and no prospectively recorded patient reported outcomes were obtained; thus, adverse events may be underreported and their true severity not represented accurately. The number of patients included in this study is small, and target delineation for RT boost was variable, which limited generalizable conclusions about survival and tumor control. Similarly, because patients were analyzed in a retrospective manner, determining how well these patients represent all patients with clinically suspicious PSW LN is difficult.

We are unable to definitively answer the critical question of whether an RT boost increases peri-and postoperative complications or improves local control. A prospective phase 1/2 trial is needed to answer these questions and under consideration at our institution.

Conclusions

Our data are hypothesis-generating and suggest that an integrated RT boost up to 60.2 Gy in 28 fractions may be well tolerated. This approach is worthy of further

exploration in prospective trials. As interest in augmenting neoadjuvant therapy in stage II-III rectal cancer increases, determining the safety and efficacy of definitive chemoradiotherapy to clinically involved extramesorectal lymph nodes is important.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7-30.
2. Sugihara K, Kobayashi H, Kato T, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. *Dis Colon Rectum*. 2006;49:1663-1672.
3. Kinugasa T, Akagi Y, Ochi T, et al. Lateral lymph-node dissection for rectal cancer: Meta-analysis of all 944 cases undergoing surgery during 1975-2004. *Anticancer Res*. 2013;33:2921-2927.
4. Watanabe T, Muro K, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol*. 2018;23:1-34.
5. Koch M, Kienle P, Antolovic D, Buchler MW, Weitz J. Is the lateral lymph node compartment relevant? *Recent Results Cancer Res*. 2005;165:40-45.
6. Fujita S, Mizusawa J, Kanemitsu Y, et al. Mesorectal excision with or without lateral lymph node dissection for clinical stage II/III lower rectal cancer (JCOG0212): A multicenter, randomized controlled, noninferiority trial. *Ann Surg*. 2017;266:201-207.
7. Fujita S, Akasu T, Mizusawa J, et al. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): Results from a multicentre, randomised controlled, non-inferiority trial. *Lancet Oncol*. 2012;13:616-621.
8. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731-1740.
9. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345:638-646.
10. Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med*. 1997;336:980-987.
11. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol*. 2005;23:5644-5650.
12. Group MS, Shihab OC, Taylor F, et al. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. *Br J Surg*. 2011;98:1798-1804.
13. Yano H, Moran BJ. The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. *Br J Surg*. 2008;95:33-49.
14. Georgiou P, Tan E, Gouvas N, et al. Extended lymphadenectomy versus conventional surgery for rectal cancer: A meta-analysis. *Lancet Oncol*. 2009;10:1053-1062.
15. Sugihara K, Moriya Y, Akasu T, Fujita S. Pelvic autonomic nerve preservation for patients with rectal carcinoma. *Cancer*. 1996;78:1871-1880.
16. Park JA, Choi GS, Park JS, Park SY. Initial clinical experience with robotic lateral pelvic lymph node dissection for advanced rectal cancer. *J Korean Soc Coloproctol*. 2012;28:265-270.
17. Kusters M, Beets GL, van de Velde CJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. *Ann Surg*. 2009;249:229-235.
18. Kim TH, Jeong SY, Choi DH, et al. Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection. *Ann Surg Oncol*. 2008;15:729-737.
19. Kim TG, Park W, Choi DH, et al. Factors associated with lateral pelvic recurrence after curative resection following neoadjuvant chemoradiotherapy in rectal cancer patients. *Int J Colorectal Dis*. 2014;29:193-200.
20. Lim SB, Yu CS, Kim CW, et al. Clinical implication of additional selective lateral lymph node excision in patients with locally advanced rectal cancer who underwent preoperative chemoradiotherapy. *Int J Colorectal Dis*. 2013;28:1667-1674.
21. Ogura A, Konishi T, Cunningham C, et al. Neoadjuvant (chemo) radiotherapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. *J Clin Oncol*. 2019;37:33-43.
22. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. *J Natl Compr Canc Netw*. 2014;12:513-519.