

# Does a fine line exist between regional and metastatic pelvic lymph nodes in rectal cancer—striking discordance between national guidelines and treatment recommendations by US radiation oncologists

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**Background:** Management of rectal cancer with involved lateral pelvic lymph nodes (LPLNs) at the time of diagnosis—the stage we refer institutionally to as Stage 3.5—is controversial. The American Joint Committee on Cancer's 7<sup>th</sup> edition classifies internal iliac lymph nodes (LNs) as regional (Stage III), but both external and common iliac LNs as metastatic (Stage IV). However, in many Asian countries all LPLNs are considered regional and patients are treated with curative intent, with literature supporting improved outcomes with LPLN dissection. Management patterns of these patients by US radiation oncologists (ROs) are unknown.

**Methods:** American ROs completed an anonymous institutional review board-approved online questionnaire regarding rectal cancer management.

**Results:** Among the 220 completed responses, 45% treat more than 10 patients annually and 39% work in academia. We found 10.5% and 34.2% recommend biopsy of clinically involved internal and common iliac LNs, respectively. The vast majority of responders—98.6% and 94.5%—treat involved internal and common iliac LNs with curative intent, respectively. Respondents recommend treatment intensification to involved internal iliac LNs by dissection of the nodal basin (88.2%) and radiation therapy (RT) boost (59.1%), and treatment intensification to involved common iliac LNs by LN dissection (76.4%) and RT boost (63.6%).

**Conclusions:** Our analysis reveals that the vast majority of US ROs approach patients with involved LPLNs, both regional (internal iliac) and metastatic (common iliac), with curative intent. They recommend treatment intensification with surgical resection and/or RT boost to involved nodes. Prospective clinical trials need to determine the appropriate management of patients with Stage 3.5 rectal cancer.

**Keywords:** Radiation oncology; rectal neoplasms; intention; lymph node excision; guideline adherence

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## Introduction

Approximately 40,000 patients are diagnosed with rectal

cancer in the United States annually (1). The standard of care for locally advanced Stage II (T3–T4, N0, M0) and Stage III (Tany, N+, M0) rectal cancer, based on

the results of a randomized German rectal trial (2), is preoperative chemoradiation therapy, followed by total mesorectal excision (TME) and additional adjuvant chemotherapy—with the goal of achieving greater than 60% of 5-year disease-free survival. In contrast, patients with metastatic disease are treated less aggressively, with the goal of prolonging survival and decreasing disease-related symptoms, but rarely with a curative intent.

Pelvic lymph nodes (LNs) outside of the mesorectum—internal iliac, external iliac, obturator, and common iliac (3)—are termed lateral pelvic lymph nodes (LPLNs). Rectal cancer with involved LPLNs is managed differently in the US compared to several countries in Asia. In the US, the American Joint Committee on Cancer (AJCC) defines only the internal iliac LN as regional (4), whereas external and common iliac LNs are considered sites of metastatic disease (5). On the other hand, in Japan all LPLNs are considered regional and patients are treated with curative intent (6).

Based on the MERCURY trial (7), as many as 10% of patients diagnosed with non-metastatic rectal cancer are found to have suspicious pelvic lymph nodes on diagnostic pelvic MRI. Current National Comprehensive Cancer Network (NCCN) guidelines recommend the inclusion of the primary tumor with pre-sacral and internal iliac LNs in the radiation treatment fields, whereas management of external and common iliac LNs is not specifically discussed, leading clinicians to assume that no chemoradiation therapy should be used in the management of rectal cancer patients with clinical involvement of these non-regional LNs (8). At the same time, radiation oncologists (ROs) routinely treat external and common iliac LNs in patients with other various pelvic malignancies. Therefore, we hypothesized that despite the current AJCC staging and NCCN guidelines, some ROs in the United States may approach patients with involvement of any LPLNs—both regional and non-regional—with curative intent. Institutionally, we coined the term “Stage 3.5” for rectal cancer patients with involved LPLNs—to highlight the uncertainty surrounding proper management of these patients.

## Methods

### *Survey instrument development and data collection*

We designed an online survey using REDCap software licensed by the Oregon Clinical and Translational Research Institute (OCTRI). The study was approved by the Oregon Health & Science University Institutional Review Board. The survey consisted of 14 questions pertaining to respondents'

demographics and use of imaging modalities. The online survey was sent anonymously by the REDCap data collecting software to 6,949 potential participants. Email invitations were sent in batches on November 16<sup>th</sup> and 17<sup>th</sup> of 2016 and a single reminder email was sent on November 30<sup>th</sup>, 2016.

### *Statistical analysis*

Respondent characteristics (years in practice, practice setting, region of practice, number of rectal patients treated per year, and preferred utilization of imaging modalities) were tested for associations with respondents' self-assessed approach to Stage 3.5 rectal cancer using Chi-squared or Fisher's Exact test, as indicated. A P of less than 0.05 was defined as statistically significant. Staging 75% or more of rectal cancer patients with a given imaging modality was defined as high utilization. R [version 3.3.3 (2017-03-06)] was used for all data analysis.

## Results

### *Respondent characteristics*

Of the 6,949 email addresses, many belonged to the same physicians, who were registered in our database with both personal and institutional email accounts, making the determination of the response rate highly inaccurate. We received 337 failed/undelivered automatic responses, seven non-applicable/ineligible responses and 220 completed responses. The characteristics of these 220 individuals are summarized in *Table 1*. Sixty percent of respondents have practiced over 10 years since completion of residency training, 61% work in private practice, and 55% treat 10 or fewer patients with rectal cancer per year.

### *Recommendations regarding biopsy of pelvic LNs*

Among respondents, 10.5% recommend biopsy of the clinically involved internal iliac LN and 34.2% for the common iliac LN (*Figure 1*). A practice with a higher volume of rectal cancer patients, defined as seeing more than ten patients per year, was associated with a lower likelihood of internal LN biopsy recommendation (P=0.019) and a trend of lower likelihood of external LN biopsy recommendation (P=0.054). High MRI utilizers were also less likely to recommend the biopsy of the internal LN (P=0.010), but not of the common LN (P=0.365), as seen in *Table 2*.

**Table 1** Characteristics of radiation oncologists who completed the survey

Respondent characteristics	Number of respondents, n [%]
Number of years after completion of residency training	
Currently in residency training	9 [4]
1–5	42 [19]
6–10	36 [16]
over 10	133 [61]
Number of rectal cancer patients evaluated over the past 12 months*	
0	3 [1]
1–5	45 [21]
6–10	73 [33]
>10	98 [45]
Practice setting	
Academic center	85 [39]
Private practice	135 [61]
Practice region*	
Northern	34 [16]
Pacific	49 [22]
Southern	42 [19]
Western	51 [23]
Central	40 [18]
Outside US	3 [1]

\*, one respondent failed to answer demographic questions concerning number of patients seen annually and region of practice.

### ***Curative intent for rectal cancer patients with involved LPLNs need treatment intensification***

There are 98.6% and 94.5% of respondents who approach rectal cancer patients with involved internal and common iliac LNs with curative intent, respectively, as shown in *Figure 1*. Among these respondents, 51.2% and 47.8% recommend combination of RT boost and pelvic lymph node dissection for involved internal iliac and common iliac LNs, respectively.

Only 3.7% and 5.3% of those respondents who approach patients with involved internal and common iliac LNs with curative intent, respectively, do not recommend any treatment intensification beyond the standard of care for locally advanced rectal cancer.

High PET/CT utilizers were more likely to recommend RT boost to involved common iliac LNs (70.9% *vs.* 57.3%,  $P=0.036$ ), as shown in *Table 3*.

Among our respondents, 88.2% recommend surgical lymph node dissection of internal iliac LNs and 59.1% recommend RT boost, as shown in *Figure 1*. For common iliac LNs these percentages are 76.4% and 63.6% for surgical *vs.* RT boost treatment intensification, respectively. Respondents who practice in private clinics are more likely to recommend surgical dissection of involved common iliac LNs at the time of TME than academic physicians (81.5% *vs.* 62.8%,  $P=0.024$ ), with a trend for a similar association for surgical management of internal iliac LN ( $P=0.09$ ) as shown in *Table 4*.

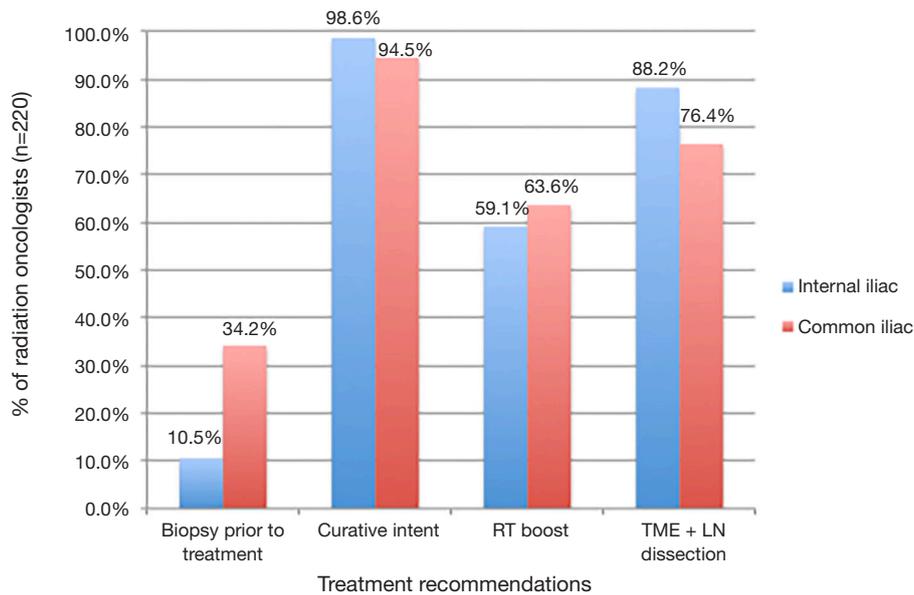
## **Discussion**

### ***Biopsy confirmation of clinically involved LPLNs in patients with rectal cancer***

Previous studies have discouraged LN biopsy in rectal cancer patients given the high rate of false negatives (3–12%) in the setting of T3/T4 primary rectal tumor (9). However, there is a significant lack of clinical experience and guidance regarding biopsy of clinically suspicious lateral pelvic lymph nodes in these patients. This is becoming a common clinical scenario with increasing pelvic MRI utilization; among patients diagnosed with rectal cancer who have no evidence of distant metastases, as many as 10% are found to have clinically suspicious LPLNs (7). Among our respondents, those who frequently evaluate rectal cancer patients, defined as practice with more than ten rectal cancer patients per year, felt more comfortable treating patients without biopsy of suspicious internal LNs. The same association was noted for respondents who frequently utilize pelvic MRI for staging of rectal cancer. Further clinical studies are critical to determine if pathological confirmation of suspicious LPLNs would allow clinicians to personalize treatment for patients, without excess toxicity. Novel imaging modalities, such as USPIO-MRI, are currently being evaluated as non-invasive modalities with higher sensitivity and specificity over routine pelvic MRI (Clinicaltrials.gov identifier for MRI-USPIO rectal cancer protocol at OHSU Knight Cancer Institute: NCT03280277).

### ***Dramatic discordance between NCCN guidelines and current practice patterns of US ROs***

Our survey results show that practicing ROs in the United



**Figure 1** Treatment recommendations by US radiation oncologists in the setting of clinically involved LPLNs in patients with rectal cancer. LPLNs, lateral pelvic lymph nodes. TME, total mesorectal excision. RT boost, radiation therapy boost.

**Table 2** Internal and common LN biopsy recommendations by respondents' characteristics

Respondent characteristics	Internal iliac LN biopsy			Common iliac LN biopsy		
	No, n (%)	Yes, n (%)	P*	No, n (%)	Yes, n (%)	P*
Practice setting			0.959			0.513
Academic	76 (89.4)	9 (10.6)		53 (63.1)	31 (36.9)	
Private practice	121 (89.6)	14 (10.4)		91 (67.4)	44 (32.6)	
Years post residency			0.065			0.314
10 or fewer years	82 (94.3)	5 (5.7)		60 (69.8)	26 (30.2)	
>10 years	115 (86.5)	18 (13.5)		84 (63.2)	49 (36.8)	
Number rectal cancer patients evaluated over a year			0.019			0.054
10 or fewer patients	103 (85.1)	18 (14.9)		72 (60.0)	48 (40.0)	
>10 patients	93 (94.9)	5 (5.1)		71 (72.4)	27 (27.6)	
EUS			0.650			0.611
Low utilizers	95 (90.5)	10 (9.5)		70 (67.3)	34 (32.7)	
High utilizers	101 (88.6)	13 (11.4)		73 (64.0)	41 (36.0)	
MRI			0.010			0.365
Low utilizers	117 (85.4)	20 (14.6)		87 (63.5)	50 (36.5)	
High utilizers	80 (96.4)	3 (3.6)		57 (69.5)	25 (30.5)	
PET/CT			0.587			0.102
Low utilizers	106 (90.6)	11 (9.4)		82 (70.7)	34 (29.3)	
High utilizers	91 (88.3)	12 (11.7)		62 (60.2)	41 (39.8)	

\*, Chi-square. Significant P values are in italic. LN, lymph node.

**Table 3** Respondents' characteristics and RT boost recommendations for involved LPLNs

Respondent Characteristics	Internal iliac LN boost			Common iliac LN boost		
	No, n (%)	Yes, n (%)	P*	No, n (%)	Yes, n (%)	P*
Practice setting			0.828			0.402
Academic	34 (40.0)	51 (60.0)		28 (32.9)	57 (67.1)	
Private practice	56 (41.5)	79 (58.5)		52 (38.5)	83 (61.5)	
Years post residency			0.656			0.855
10 or fewer years	34 (39.1)	53 (60.9)		31 (35.6)	56 (64.4)	
>10 years	56 (42.1)	77 (57.9)		49 (36.8)	84 (63.2)	
Number rectal cancer patients evaluated over a year			0.634			0.535
10 or fewer patients	48 (39.7)	73 (60.3)		42 (34.7)	79 (65.3)	
>10 patients	42 (42.9)	56 (57.1)		38 (38.8%)	60 (61.2)	
EUS			0.967			0.458
Low utilizers	43 (4.0)	62 (59.0)		41 (39.0)	64 (61.0)	
High utilizers	47 (41.2)	67 (58.8)		39 (34.2)	75 (65.8)	
MRI			0.252			0.599
Low utilizers	52 (38.0)	85 (62.0)		48 (35.0)	89 (65.0%)	
High utilizers	38 (45.8)	45 (54.2)		32 (38.6)	51 (61.4%)	
PET/CT			0.092			0.036
Low utilizers	54 (46.2)	63 (53.8)		50 (42.7)	67 (57.3%)	
High utilizers	36 (35.0)	67 (65.0)		30 (29.1)	73 (70.9%)	

\*. Chi-square. Significant P value is in italic. LPLNs, lateral pelvic lymph nodes; LN, lymph node; RT, radiation therapy.

States almost uniformly approach rectal cancer patients with both internal (Stage III) and common (Stage IV) iliac LNs with curative intent, despite the current national guidelines recommendations based on AJCC staging criteria. Clinical evidence from Asian countries that embrace curative management of rectal cancer patients with LPLNs supports surgical dissection of involved pelvic lymph nodes. High incidence of LPLN metastases was reported after preoperative chemoradiation therapy—which primarily targets mesorectum and internal pelvic lymph nodes. Addition of LPLN dissection to TME was shown to decrease 3-year local recurrence rate from 7.1% down to 2.7% in one study (6) and even revealed a statistical improvement in 5-year local-recurrence-free survival in another study (10).

Our survey shows that the great majority of US ROs recommend surgical dissection of involved LPLNs, both regional (internal LN) and non-regional (common LN). Unfortunately, we did not query our respondents

whether they were aware of the Asian surgical literature to determine whether their recommendations were based on this clinical evidence or based on extrapolation from oncological management of other pelvic malignancies. Over half of respondents also recommend, and likely use in their practice, dose-intensification to the involved LPLNs by using RT boost. It is imperative to determine the appropriate management of these patients through prospective clinical trials. Until then, the national leaders in the field of rectal cancer need to draft a consensus statement regarding the appropriate management, to help practicing physicians evaluate and manage these patients safely and effectively.

### Limitations

The greatest limitation of our study is a low response rate. It is likely that response bias could have introduced a misrepresentation into actual current patterns of care in the

**Table 4** Respondents' characteristics and recommendations for involved LPLN dissection at the time of TME

Respondent characteristics	Internal iliac LN dissection + TME			Common iliac LN dissection + TME		
	No, n (%)	Yes, n (%)	P*	No, n (%)	Yes, n (%)	P*
Practice setting			0.090			<i>0.024</i>
Academic	14 (16.5)	71 (83.5)		27 (31.8)	58 (68.2)	
Private practice	12 (8.9)	123 (91.1)		25 (18.5)	110 (81.5)	
Years post residency			0.759			0.855
10 or fewer years	11 (12.6)	76 (87.4)		20 (23.0)	67 (77.0)	
>10 years	15 (11.3)	118 (88.7)		32 (24.1)	101 (75.9)	
Number rectal cancer patients evaluated over a year			0.790			0.296
10 or fewer patients	15 (12.4)	106 (87.6)		32 (26.4)	89 (73.6)	
>10 patients	11 (11.2)	87 (88.8)		20 (20.4)	78 (79.6)	
EUS			0.995			0.734
Low utilizers	12 (11.4)	93 (88.6)		26 (24.8)	79 (75.2)	
High utilizers	13 (11.4)	101 (88.6)		26 (22.8)	88 (77.2)	
MRI			0.436			0.391
Low utilizers	18 (13.1)	119 (86.9)		35 (25.5)	102 (74.5)	
High utilizers	8 (9.6)	75 (90.4)		17 (20.5)	66 (79.5)	
PET/CT			0.729			0.913
Low utilizers	13 (11.1)	104 (88.9)		28 (23.9)	89 (76.1)	
High utilizers	13 (12.6)	90 (87.4)		24 (23.3)	79 (76.7)	

\*, Chi-square. Significant P value is in italic. LPLN, lateral pelvic lymph node; TME, total mesorectal excision.

United States. Unfortunately, all claim-based retrospective studies would not be able to capture the most up-to-date snapshot of real-time practice patterns and would require several years of data capture and analysis to shed light on this important question.

## Conclusions

Our survey-based analysis of current practice patterns among US ROs reveals a dramatic discordance between the national guidelines and treatment recommendations for Stage 3.5 rectal cancer patients—those with involved LPLNs, but in the absence of distant metastases. The overwhelming majority of practicing ROs approach these patients with curative intent. Moreover, against the national guidelines that recommend treatment de-intensification in the non-curative setting, most practicing ROs in the

US recommend treatment intensification, in the form of involved pelvic LN dissection, RT boost or both. The management of Stage 3.5 rectal cancer patients with involved LPLNs is currently not based on robust clinical evidence, and prospective clinical studies are greatly needed to establish the most appropriate management of these patients. Until this data is known, consensus guidelines must be issued by clinician-leaders in the field of rectal cancer to guide practicing oncologists to deliver safe and effective treatment to patients with Stage 3.5 rectal cancer.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by institutional review board of Oregon Health and Science University (IRB protocol 11149), and the requirement to obtain informed consent from survey respondents was waived.

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