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ORIGINAL ARTICLE

Lymph Node Harvest After Neoadjuvant Treatment for Rectal Cancer and Its Impact on Oncological Outcomes

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Abstract

The aim of this study was to analyze the influence of neoadjuvant treatment on nodal harvest after rectal cancer surgery and its impact on long-term oncological outcomes. A retrospective analysis of patients with rectal cancer who received curative intent treatment from 2002 to 2012 in our institution was performed. Data on various clinic-pathological and treatment details were recovered from the records. The number of nodes harvested after surgery was analyzed. The influence of number of nodes harvested on overall survival and disease free survival was analyzed. Among the 459 patients included in this study, 326 underwent surgery after neoadjuvant treatment (NAT). The mean number of nodes harvested was significantly lower in patients who received NAT compared with those who did not (8.9 ± 5.77 vs 14 ± 9.84, $p < 0.001$). However, the mean number of pathologically positive nodes was not significantly different. A minimum of 12 nodes were harvested in only 27.9% of patients who received NAT. No lymph nodes were identified in the specimen in 15 patients (4.6%) who underwent surgery after NAT. The only independent factors influencing harvest of a minimum of 12 nodes were patient age and NAT. The 5-year overall survival was not significantly different in patients in whom < 12 or ≥ 12 nodes were harvested (64% vs 69% respectively, $p = 0.5$). Neoadjuvant chemoradiation significantly reduces nodal harvest in patients undergoing treatment for rectal cancer. However, this reduced nodal harvest did not adversely impact survival in patients. However, every effort must be made by the surgeon and the pathologist to maximize the nodal harvest.

Keywords Rectal cancer · Neoadjuvant chemoradiation · Surgery · Nodal harvest · Survival

Introduction

Neoadjuvant chemoradiation (NCRT) is standard of care in locally advanced rectal cancer as it improves local control and improves sphincter preservation [1]. Pathological nodal status is considered to be one of the most important prognostic factors for patients undergoing surgery for carcinoma rectum after NCRT [2], and the oncological outcome in node negative patients significantly improves as an increasing number of nodes are examined [3]. The American Joint Committee on Cancer (AJCC) staging manual recommends examination of a minimum of 12 nodes for accurate staging of rectal cancer surgery [4]. Various factors determine the nodal harvest after surgery for rectal cancer [5, 6]. Besides the quality of the surgery and of the pathological examination, other patient and treatment-related factors also influence the nodal harvest.

The aim of this study was to determine the influence of neoadjuvant treatment (NAT) for rectal cancer on nodal harvest and analyze the influence of number of harvested nodes on oncological outcomes.

Patients and Methods

This is a retrospective analysis of patients who were treated for adenocarcinoma of the rectum from 2002 to 2012 in our institution. Patients with non-metastatic rectal cancer who were treated with a curative intent were included in this study. Patients were staged using a contrast enhanced CT scan of

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abdomen and pelvis along with chest X-ray. Patients with locally advanced rectal cancer (cT3/T4 or node positive) underwent NAT using radiation with or without addition of chemotherapy (5-fluorouracil) followed by radical surgery. Dose of radiation used was 50.4 Gy in 25 fractions. Patients with early stage tumors underwent direct surgery except in low lying cT2 tumors where NAT was offered with the aim of sphincter preservation. The resected specimen was fixed in formalin and subjected to standard histopathological examination [7]. Nodes were identified first by digital palpation and then using a lymph node revealing solution.

Adjuvant chemotherapy was offered to all patients who received NCRT. Patients were kept on surveillance after completion of treatment. Clinical examination and serum carcinoembryonic antigen (CEA) measurements were done every 3 months for the first 3 years, every 6 months for the next 2 years and annually thereafter. A CT scan of the abdomen and pelvis and a chest X-ray was done annually for the first 3 years and when clinically indicated thereafter.

The demographic, tumor, and treatment-related data were retrieved from the records. The histopathology reports were reviewed to determine the nodal yield and other pathological details. The impact of NAT on the nodal yield was analyzed using logistic regression score. The influence of the number of nodes harvested on the overall survival (OS) and disease-free survival (DFS) was studied using actuarial method depicting results with Kaplan–Meier plots. We tried to determine a cut-off value of minimum nodes harvested after NAT that would predict a difference in survival.

Results

A total of 474 patients with rectal cancer underwent treatment during this period of which consecutive patients who underwent a curative intent treatment were included in this study. Neoadjuvant treatment was offered to 326 patients (293 patients received NCRT and 33 patients received only radiation), while 133 patients underwent direct surgery. The demographic, treatment, and pathological characteristics of patients who underwent surgery after neoadjuvant treatment are depicted in Table 1. Lower rectal tumors were more common (50.4%) than middle and upper rectal tumors. Most of the tumors were T3 (56.6%).

The mean number of nodes harvested in patients who received NAT was significantly lower than that in those who did not receive NAT (8.9 ± 5.77 (standard deviation) vs 14 ± 9.84, respectively, $p < 0.001$). Similarly, the mean total nodes harvested in patients who had a pN0 disease and pN+ disease was also significantly lower in patients who received NAT compared with those who underwent upfront surgery (7.4 ± 4.8 vs

Table 1 Demographic variables and tumor characteristics

Variable	Distribution
Median age in years (range)	52 (16–85)
Sex	
Male	283 (61.7%)
Female	176 (38.3%)
Location of tumor	
Upper rectum	22 (4.8%)
Middle rectum	186 (40.5%)
Lower rectum	251 (50.4%)
Histology	
Adenocarcinoma	379 (82.6%)
Mucinous adenocarcinoma	47 (10.2%)
Signet ring type adenocarcinoma	16 (3.5%)
Poorly differentiated carcinoma	17 (3.7%)
Clinical T stage	
T1	6 (1.3%)
T2	83 (18.1%)
T3	260 (56.6%)
T4	38 (8.3%)
TX	75 (15.7%)
Clinical N stage	
N0	184 (40.1%)
N1	166 (36.2%)
N2	13 (2.8%)
NX	96 (20.9%)
Neoadjuvant therapy	
None	133 (29%)
Radiation	33 (7.2%)
Chemoradiation	293 (63.8%)
Surgery	
Abdominoperineal resection	251 (54.7%)
Sphincter preserving surgery	208 (45.3%)
Approach to surgery	
Laparoscopic	86 (18.7%)
Open	373 (81.3%)
Pathological T stage	
p T0	42 (9.2%)
p TIS	3 (0.7%)
p T1	15 (3.3%)
p T2	105 (22.9%)
p T3	264 (57.5%)
p T4	30 (6.5%)
Pathological N stage	
p N0	257 (55.9%)
p N1	94 (20.4%)
p N2	93 (20.3%)
p Nx (no nodes identified)	15 (4.6%)

Table 2 Univariate analysis of factors influencing harvest of a minimum of 12 nodes

Variable	HR	95% confidence interval	*p* value
Age			
Less than or equal to 49 years	1		
More than 49 years	0.623	0.423–0.917	0.016
Sex			
Male	1		
Female	1.141	0.770–1.689	0.511
Distance from anal verge			
Upper and mid rectum	1		
Lower rectum	1.473	1.002–2.165	0.049
Tumor histology			
Adenocarcinoma	1		
Mucinous adenocarcinoma	1.924	1.045–3.543	0.036
Signet ring type adenocarcinoma	2.008	0.736–5.475	0.173
Poorly differentiated carcinoma	0.618	0.197–1.933	0.408
Neoadjuvant treatment			
Chemoradiation	1		
Radiation	0.965	0.430–2.164	0.931
No	2.859	1.869–4.375	< 0.001
Type of surgery			
Sphincter preserving surgery	1		
Abdominoperineal resection	0.679	0.462–0.998	0.049
Surgical approach			
Open	1		
Laparoscopic	0.622	0.369–1.047	0.074
Interval between RT ad surgery			
Less than or equal to 50 days	1		
More than 50 days	0.540	0.365–0.798	0.002
Pathologic T stage			
T1	1		
T2	1.062	0.242–4.673	0.936
T3	2.814	1.250–6.335	0.012
T4	3.719	1.298–10.653	0.014
TIS	0.850	0.198–3.658	0.827
T0	2.035	0.851–4.867	0.110

13 ± 9.1, $p < 0.001$, and 10.9 ± 6.4 vs 15.3 ± 10.6, $p + 0.001$ respectively). A minimum of 12 nodes were harvested from the specimen in only 27.9% of patients who received NAT compared with 52.6% of patients undergoing direct surgery. No lymph nodes were identified in the specimen of 15 patients who underwent surgery after NAT.

On univariate analysis of factors influencing nodal harvest, age ≤ 49 years, sphincter preserving surgery, less than 50-day interval between NAT and surgery, upper and middle rectal tumors, no neoadjuvant treatment, mucinous adenocarcinomas, and pT3/T4 tumors were all associated with a significantly higher chance of harvesting at least 12 nodes (Table 2). However, on multivariate analysis only age $\leq$ 49 years and no neoadjuvant treatment had an independent effect on harvesting a minimum of 12 nodes (Table 3).

There was no significant difference in the 5-year DFS or OS in patients who received NAT when different cut-off values of the number of harvested nodes ranging from 0 to 12 were used (Table 4). A nodal harvest of less than 12 nodes did not adversely affect the survival (Fig. 1). The 5-year DFS and OS of patients in whom no nodes were harvested after NAT was not significantly different

Table 3 Multivariate analysis of factors influencing harvest of a minimum of 12 nodes

Variable	HR	95% confidence interval	*p* value
Age			
≤ 49 years	1		
> 49 years	0.486	0.308–0.767	0.002
Distance from anal verge			
Upper and middle rectum	1		
Lower rectum	1.209	0.664–2.199	0.535
Tumor histology			
Adenocarcinoma	1		
Mucinous adenocarcinoma	1.819	0.925–3.577	0.083
Signet ring type adenocarcinoma	2.493	0.878–7.078	0.086
Poorly differentiated carcinoma	0.672	0.200–2.250	0.519
Neoadjuvant treatment			
Chemoradiation	1		
Radiation	1.260	0.531–2.990	0.601
None	3.644	1.952–6.804	< 0.001
Type of surgery			
Sphincter preserving surgery	1		
Abdominoperineal resection	0.874	0.477–1.602	0.664
Interval between radiation and surgery			
≤ 50 days	1		
> 50 days	0.922	0.531–1.602	0.773
T stage			
T1	1		
T2	0.633	0.131–3.067	0.570
T3	2.196	0.938–5.144	0.070
T4	2.358	0.761–7.307	0.137
TIS	0.329	0.368–1.591	0.167
T0	1.451	0.570–3.695	0.435

from that of patients who had at least 1 node harvested (OS 70% vs 65%, respectively, $p = 0.44$) or from that of patients who a pathological N0 status (OS 70% vs 73%, respectively, $p = 0.19$) (Fig. 1).

Discussion

We have shown that the number of nodes harvested in patients undergoing surgery for rectal cancer after NAT is significantly less when compared with those who undergo direct surgery. A similar finding has been reported by other authors [5, 8–11]. In an analysis of more than 1200 patients with rectal cancer, Mekenkamp et al. [5] reported that neoadjuvant radiation significantly lowered the nodal yield (6.9 vs 8.5, $p < 0.0001$). A systematic review and meta-analysis concluded that the number of nodes harvested and the number of positive nodes in patients who undergo surgery after neoadjuvant CRT are less compared with patients who did not receive neoadjuvant treatment [8]. It has been estimated that the nodal harvest in rectal cancer will reduce by 0.21% for every 1 Gy of radiation [11].

Although the latest AJCC cancer staging manual (8th edition) recommends examination of a minimum of 12 nodes for accurate staging after rectal cancer surgery, it recognizes that the number of nodes examined may be less in patients receiving pre-operative radiation [4]. Our observation that only 27.9% of patients undergoing NAT have at least 12 nodes harvested is in agreement with this statement. Other studies have reported that 20–70.4% of patients receiving neoadjuvant CRT had fewer than 12 lymph nodes harvested [9, 10, 12].

The nodal harvest after rectal cancer surgery is influenced by modifiable (surgery/surgeon and pathologist related) and non-modifiable (patient and disease related) factors [5, 13]. Surgeon-related factors include specialization and experience

Table 4 Survival based on the number of nodes harvested in patients who received neoadjuvant treatment

Number of nodes harvested	5-year DFS	*p* value	5-year OS	*p* value
0	63	0.551	70	0.441
≥ 1	50		65	
< 2	60	0.642	66	0.423
≥ 2	50		65	
< 3	47	0.093	58	0.203
≥ 3	51		66	
< 4	53	0.206	60	0.174
≥ 4	50		66	
< 5	54	0.487	61	0.492
≥ 5	50		66	
< 6	51	0.358	61	0.279
≥ 6	50		67	
< 7	49	0.200	62	0.271
≥ 7	52		67	
< 8	52	0.937	66	0.909
≥ 8	50		64	
< 9	51	0.856	65	0.903
≥ 9	50		65	
< 10	52		64	0.997
≥ 10	49	0.804	66	
< 11	50	0.878	62	0.483
≥ 11	50		69	
< 12	50	0.900	64	0.577
≥ 12	51		69	

DFS disease-free survival, *OS* overall survival

of the surgeon. We have earlier shown that the number of nodes harvested does not significantly differ when surgery is performed for rectal cancer by an open or laparoscopic approach after CRT [14]. Although few studies reported that lymph node harvest varied according to the reporting pathologist [5, 15], both the quality of the surgery and the pathological examination are important in determining the nodal yield [6]. Various methods like fat-dissolving solutions, intra-arterial injection of a staining agent like methylene blue, and exhaustive submission of mesenteric fat have been shown to improve the nodal yield although the clinical relevance of these methods is controversial given the fact that they are time and labor intensive [13, 16].

The modifiable factors in this study were controlled since all surgeries in this study, performed in a high volume centre, were done or supervised by surgeons experienced in rectal cancer resections and the pathological examination was also performed or supervised by experienced pathologists following a standard protocol. Although factors like increasing T stage, tumor location, and interval to surgery have also been previously reported to influence nodal harvest, these factors did not retain significance in a multivariate analysis in our study. The only independent predictors of nodal harvest in our study were non-modifiable factors related to the patient (younger age) or the treatment (use of NAT). The influence of age and use of NAT on nodal harvest has been reported previously [5, 6, 15].

The use of neoadjuvant radiation leads to an inflammatory reaction causing stromal fibrosis and a reduction in the size of the nodes, leading to difficulty in identifying them in the resected specimen [5, 12]. In our study, no nodes were identified in the resected specimen in a small proportion of patients (4.6%) and the survival of these patients were not significantly different from the pathologically node negative patients (pN0). The reported incidence of the absence of nodes in the resected specimen after neoadjuvant CRT in rectal cancer varies from 3.4–16% [10, 17–19]. However, similar to our study, none of these studies have shown an inferior oncological outcome if no nodes were harvested. Rather, it is believed that an absence of nodes in the specimen represents a good response to neoadjuvant CRT [17].

Although the survival of patients in whom < 12 nodes were harvested was not significantly different from those with a higher nodal yield in our study, we were unable to identify a cut off number of nodes harvested after CRT that would predict a difference in the oncological outcomes. In contrast, Mekenkamp et al. [5] suggested that at least 8 nodes be harvested in rectal cancer patients post-CRT since the recurrence free interval was lower in node negative patients if less than 8 nodes were identified. Other authors have also reported that a reduced nodal harvest or failure to identify a minimum of 12 nodes after neoadjuvant CRT did not result in an inferior oncological outcome [9–11, 18, 20].

The limitations of this study include its retrospective nature and the lack of pathology review of all archived slides for the purpose of this study. However, the protocols followed for surgery and pathological examination have more or less remained unchanged throughout the study duration in our institution as have the surgeons and pathologists involved in the treatment.

Conclusion

The number of nodes harvested after neoadjuvant treatment for rectal cancer is less than that after direct surgery, and the minimum prescribed number of 12 nodes was harvested in only a small proportion of patients although this was not associated with an inferior survival. However, every effort must be made by the surgeon and the pathologist to maximize the nodal harvest.

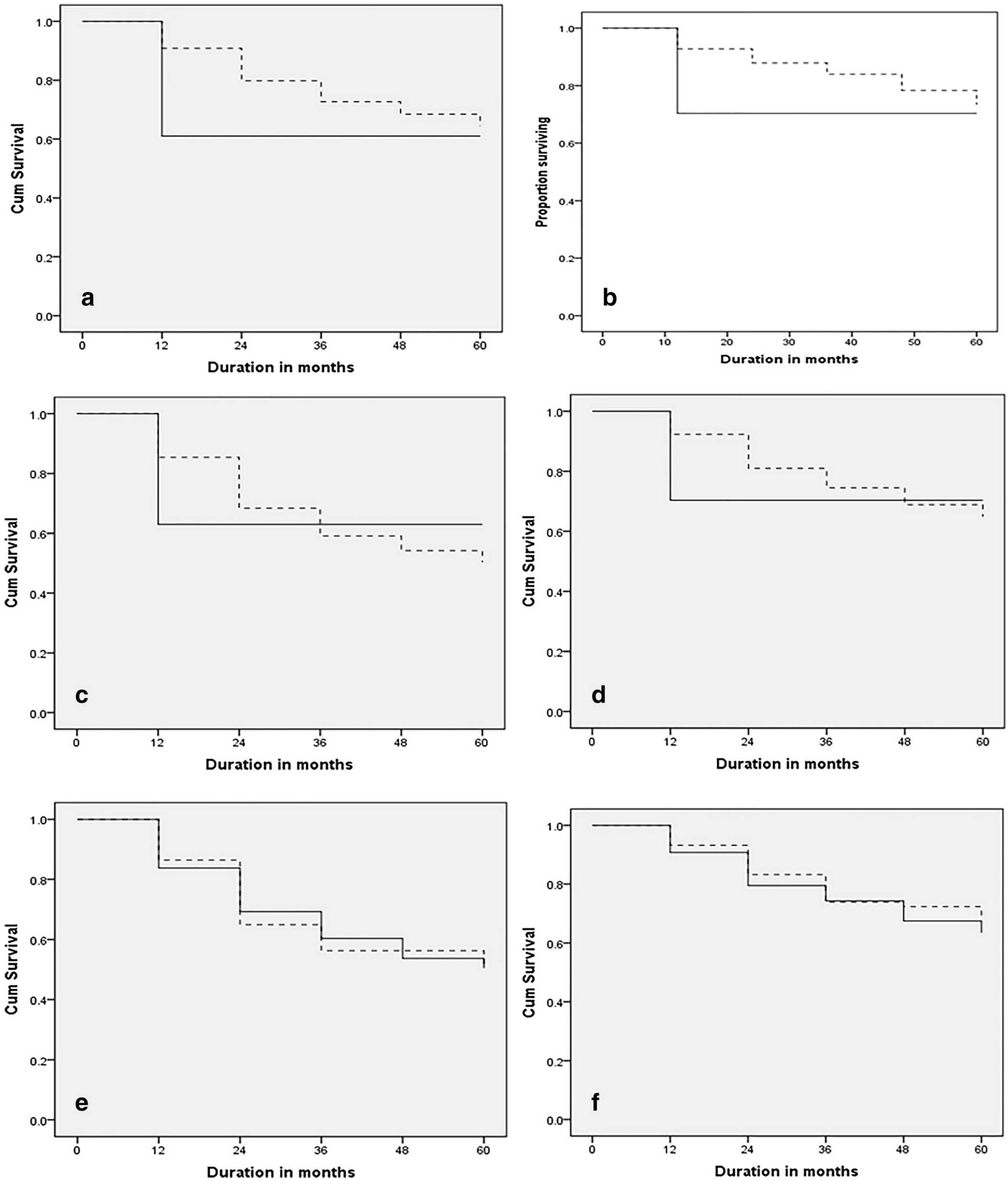

Fig. 1 Kaplan-Meier curves showing comparison of **a**) disease-free survival and **b**) overall survival of patients with zero nodes harvested (straight line) vs pathological node negative patients (dotted line); **c**) disease-free survival and **d**) overall survival of patients with zero nodes harvested (straight line) vs patients in whom at least one node was harvested (dotted line); **e**) disease-free survival and **f**) overall survival of patients in whom <12 nodes (straight line) or ≥12 nodes (dotted line) were harvested

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References

1. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R (2004) German rectal cancer study G. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351(17):1731–1740. https://doi.org/10.1056/NEJMoa040694
2. Kim TH, Chang HJ, Kim DY, Jung KH, Hong YS, Kim SY, Park JW, Oh JH, Lim SB, Choi HS, Jeong SY (2010) Pathologic nodal classification is the most discriminating prognostic factor for disease-free survival in rectal cancer patients treated with preoperative chemoradiotherapy and curative resection. Int J Radiat Oncol Biol Phys 77(4):1158–1165. https://doi.org/10.1016/j.ijrobp.2009.06.019
3. Tepper JE, O'Connell MJ, Niedzwiecki D, Hollis D, Compton C, Benson AB 3rd, Cummings B, Gunderson L, Macdonald JS, Mayer RJ (2001) Impact of number of nodes retrieved on outcome in patients with rectal cancer. J Clin Oncol 19(1):157–163. https://doi.org/10.1200/JCO.2001.19.1.157
4. Milburn Jessup J, Richard M. Goldberg, Elliot A. Asare et al (2017) AJCC cancer staging manual, Eighth edn. (editor in chief Mahul B. Amin), Springer USA. https://doi.org/10.1007/978-3-319-40618-3_20
5. Mekenkamp LJ, van Krieken JH, Marijnen CA, van de Velde CJ, Nagtegaal ID Pathology Review C, the Co-operative Clinical I. Lymph node retrieval in rectal cancer is dependent on many factors–the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol 33(10):1547–1553. https://doi.org/10.1097/PAS.0b013e3181b2e01f
6. Morris EJ, Maughan NJ, Forman D, Quirke P (2007) Identifying stage III colorectal cancer patients: the influence of the patient, surgeon, and pathologist. J Clin Oncol 25(18):2573–2579. https://doi.org/10.1200/JCO.2007.11.0445
7. Quirke P, Durdey P, Dixon MF, Williams NS (1986) Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 2(8514):996–999
8. Mechera R, Schuster T, Rosenberg R, Speich B (2017) Lymph node yield after rectal resection in patients treated with neoadjuvant radiation for rectal cancer: a systematic review and meta-analysis. Eur J Cancer 72:84–94. https://doi.org/10.1016/j.ejca.2016.10.031
9. Damin DC, Rosito MA, Contu PC, Tarta C, Ferreira PR, Kliemann LM, Schwartsmann G (2012) Lymph node retrieval after preoperative chemoradiotherapy for rectal cancer. J Gastrointest Surg 16(8):1573–1580. https://doi.org/10.1007/s11605-012-1916-4
10. Baxter NN, Morris AM, Rothenberger DA, Tepper JE (2005) Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. Int J Radiat Oncol Biol Phys 61(2):426–431. https://doi.org/10.1016/j.ijrobp.2004.06.259
11. Rullier A, Laurent C, Capdepont M, Vendrely V, Belleannee G, Bioulac-Sage P, Rullier E (2008) Lymph nodes after preoperative chemoradiotherapy for rectal carcinoma: number, status, and impact on survival. Am J Surg Pathol 32(1):45–50. https://doi.org/10.1097/PAS.0b013e3180dc92ab
12. Marks JH, Valsdottir EB, Rather AA, Nweze IC, Newman DA, Chernick MR (2010) Fewer than 12 lymph nodes can be expected in a surgical specimen after high-dose chemoradiation therapy for rectal cancer. Dis Colon Rectum 53(7):1023–1029. https://doi.org/10.1007/DCR.0b013e3181dadeb4
13. Li Destri G, Di Carlo I, Scilletta R, Scilletta B, Puleo S (2014) Colorectal cancer and lymph nodes: the obsession with the number 12. World J Gastroenterol 20(8):1951–1960. https://doi.org/10.3748/wjg.v20.i8.1951
14. Seshadri RA, Srinivasan A, Tapkire R, Swaminathan R (2012) Laparoscopic versus open surgery for rectal cancer after neoadjuvant chemoradiation: a matched case-control study of short-term outcomes. Surg Endosc 26:154–161. https://doi.org/10.1007/s00464-011-1844-5
15. Evans MD, Barton K, Rees A, Stamatakis JD, Karandikar SS (2008) The impact of surgeon and pathologist on lymph node retrieval in colorectal cancer and its impact on survival for patients with Dukes' stage B disease. Color Dis 10(2):157–164. https://doi.org/10.1111/j.1463-1318.2007.01225.x
16. Hamza A, Sakhi R, Khawar S, Alrajjal A, Edens J, Khurram MS, Khan U, Szpunar S, Mazzara P (2018) Role of “second look” lymph node search in harvesting optimal number of lymph nodes for staging of colorectal carcinoma. Gastroenterol Res Pract 1985031:1–6. https://doi.org/10.1155/2018/1985031
17. Habr-Gama A, Perez RO, Proscurshim I, Rawet V, Pereira DD, Sousa AH, Kiss D, Cecconello I (2008) Absence of lymph nodes in the resected specimen after radical surgery for distal rectal cancer and neoadjuvant chemoradiation therapy: what does it mean? Dis Colon Rectum 51(3):277–283. https://doi.org/10.1007/s10350-007-9148-5
18. Kim YW, Kim NK, Min BS, Lee KY, Sohn SK, Cho CH, Kim H, Keum KC, Ahn JB (2009) The prognostic impact of the number of lymph nodes retrieved after neoadjuvant chemoradiotherapy with mesorectal excision for rectal cancer. J Surg Oncol 100(1):1–7. https://doi.org/10.1002/jso.21299
19. Lee WS, Lee SH, Baek JH, Lee WK, Lee JN, Kim NR, Park YH (2013) What does absence of lymph node in resected specimen mean after neoadjuvant chemoradiation for rectal cancer. Radiat Oncol 8:202. https://doi.org/10.1186/1748-717X-8-202
20. Kim WR, Han YD, Cho MS, Hur H, Min BS, Lee KY, Kim NK (2015) Oncologic impact of fewer than 12 lymph nodes in patients who underwent neoadjuvant chemoradiation followed by total mesorectal excision for locally advanced rectal cancer. Medicine (Baltimore) 94(28):e1133. https://doi.org/10.1097/MD.0000000000001133