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ORIGINAL ARTICLE

National multicentric evaluation of quality of pathology reports for rectal cancer in France in 2016

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Abstract

The quality of pathologic assessment of rectal cancer specimens is crucial for treatment efficiency and survival. The Royal College of Pathologists (RCP) recommends evaluating the quality of the pathology report in routine practice using three quality indicators (QIs): the number of lymph nodes (LNs) analyzed (≥ 12), the rate of venous invasion (VI ≥ 30%), and peritoneal involvement (pT4a ≥ 10%). In this study, we evaluated the three QIs of the French national pathology reports and compared them with British guidelines and assessed the influence of neoadjuvant radiochemotherapy on QIs. From January 1 to December 31, 2016, all pathology reports for rectal adenocarcinoma were collected from French departments. Neoadjuvant radiochemotherapy included long-course radiotherapy with concomitant 5-FU-based chemotherapy. A total of 983 rectal cancer pathology reports were evaluated. A median of 15 LNs were analyzed and 81% of centers had ≥ 12 LNs. The rate of VI was 30% and 41% of centers had ≥ 30% VI. The rate of pT4a was 4% and 18% of centers reported ≥ 10% pT4a. None of the centers reached the threshold for the three QIs. All three QIs were lower after radiochemotherapy compared to surgery alone. In conclusion, in French routine practice, the values of two of the three QIs (LNs analyzed and VI) were globally in line with RCP guidelines. However, the rate of pT4a was very low, particularly after radiochemotherapy, suggesting its low value in rectal cancer.

Keywords Rectal cancer · Pathology report · Quality report · Neoadjuvant radiochemotherapy

Introduction

The quality of pathologic assessment of rectal cancer specimens is crucial for determining reliable prognostic criteria (such as pathological tumor–node–metastasis (pTNM), vascular invasion, circumferential resection margin (CRM), and microsatellite instability phenotype) and for establishing an efficient individual therapeutic project. To decrease the inequities of prognosis related to a lack of pathology, most of societies of pathology including the French society edit national guidelines, which are regularly revised, with detailed protocol for the examination of colorectal specimen [1–3]. All the items of the pathology report are developed without any information about the main quality indicator (QI) and the threshold to reach for quality evaluation. However, the Royal College of Pathologists (RCP) is the only national society to recommend since 2014 that multidisciplinary teams and/or pathology departments in the UK audit their reports in routine practice. Their objective is to ensure that their overall results are not significantly different from what might be expected [4–6]. In the context of quality approach of pathology department in France, it seems interesting to test the relevance of QI available in the literature in our routine practice. The RCP proposed three different QIs for such evaluation: the number of lymph nodes (LNs) analyzed, the rate of venous invasion (VI), and the rate of peritoneal involvement (pT4a). All three indicators are of prognostic value. The recommended number of LNs analyzed per specimen is 12. If the number is less than 12, the risk for developing a stage II tumor is higher than if

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more than 12 LNs are analyzed (and are negative) [7]. Several factors influence the number of LNs analyzed, including obesity, type of surgery, tumor size and stage, and neoadjuvant treatment. However, it is likely that the manner in which the pathologist examines and reports the specimen is the most important [8]. VI reflects tumor aggressiveness and must be taken into account for treatment decisions [9]. Both types of vascular invasion, lymphatic and venous, are predictive of LN metastasis and survival [5, 6, 10]. Although the RCP recommends reporting only large vessel invasion (i.e., venous invasion excluding lymphatics), the College of American Pathologists suggests reporting both and separately. In addition, both institutions recommend specifying the location of VI (intra- or extramural), even if the adverse prognosis of extramural invasion is more obvious [5, 6, 11]. Peritoneal invasion by the tumor has a negative impact on prognosis due to a high risk for peritoneal carcinomatosis [12, 13]. However, the lack of standard guidelines for assessing pT4a may contribute to underdiagnosis [11]. Neoadjuvant therapy also likely influences the rates of pT4a and possibly VI, but objective data are lacking.

This study evaluated the three QIs of the French national pathology reports, compared them with British guidelines, and assessed the influence of neoadjuvant radiochemotherapy on QIs.

Materials and methods

Design

This was a multicenter French national study focusing on quality reports of rectal cancer specimens to compare with British pathology guidelines. All pathology departments involved in the French clinical trials of rectal cancer (GRECCAR group) [14] were contacted in March 2017 to enroll rectal cancer reports performed between January 1 and December 31, 2016. Inclusion criteria were rectal adenocarcinoma treated by rectal excision with or without neoadjuvant radiochemotherapy. Exclusion criteria were rectal cancer recurrence, anal and colon cancers, and rectal cancer treated by local excision.

Data analyzed

Clinical and pathological data included tumor location from the anal verge (low 0–5, mid 6–10, and high 11–15 cm), type of surgery performed (partial vs. total mesorectal excision), neoadjuvant radiochemotherapy (50 Gy in 5 weeks with Xeloda), quality of the mesorectum [15], number of LNs analyzed, eventual secondary dissection of LNs, vascular invasion (venous or lymphatic, intra- or extramural), perineural invasion, tumor budding, CRM, TNM staging [16], and tumor regression grading (TRG). We also analyzed the number of blocks performed, the use of a template (minimum dataset recommended by the French National Cancer Institute) [2], turnaround time of the pathology report (date from the specimen receipt at the pathology laboratory or date of surgery in cases of missing information), and the number of signatory pathologists.

Endpoints

The primary objective was to evaluate the three QIs of the French national pathology reports of rectal cancer specimens (number of LNs analyzed and rates of VI and pT4a) and to compare them with the recommended thresholds of British pathologic guidelines. The standard recommendations are a median of ≥ 12 LNs examined, $\geq 30\%$ VI, and $\geq 10\%$ pT4a [4]. The secondary objective was to assess the influence of neoadjuvant radiochemotherapy on QIs.

Statistical analyses

We analyzed both the mean of events for each pathologic indicator and the frequency of centers with the recommended thresholds. Quantitative data are expressed as the mean ± standard deviation or the median with the range or interquartile range (IQR). Qualitative data are expressed as percentages. Differences between groups were determined using the χ^2 test (χ^2 modified if necessary) or Fisher's exact test and Mann–Whitney and t tests. A p value less than 0.05 was considered statistically significant.

Results

Pathology reports

Globally, 1013 pathology rectal cancer reports were enrolled from 22 French laboratories (14 public hospitals, 5 private institutions, and 3 cancer centers) over a 1-year period in 2016. Thirty cases were excluded (5 rectal cancer recurrences, 3 anal cancers, 12 colon cancers, and 10 local excisions), for a total of 983 cases analyzed. A median of 36 reports were performed per center (range 6–122). A median of 19 blocks were identified (range 1–54). A template was used as a pathology report in 59% (579/983) of cases. The turnaround time of pathology reports was 10 (range 2–38) calendar days. There was a median of four signatory pathologists per center (range 1–18).

Overall rectal specimens

Characteristics of rectal tumors, overall and according to treatment, are presented in Table 1. Rectal tumors were located as

follows: 35% in the lower third region, 27% in the middle region, and 17% in the highest region. However, location was not specified in 21% of cases. Overall, a median of 15 LNs were retrieved from each specimen (IQR 11–21) and 81% of centers reported ≥ 12 LNs (18/22) (Fig. 1). In all, 30% of specimens had VIs (292/983) and 41% of centers reported ≥ 30% VIs (9/22); 4% of specimens had pT4a (42/983) and 18% of centers reported ≥ 10% pT4a (4/22). Overall, no center reached the threshold for the three QIs (Fig. 2a).

When VI was present, the type of structure involved (lymphatic or vein) was mentioned in 27% (78/292) of cases. An extramural location was noted in 36% (107/292) of cases. In 5% (45/983) of cases, complementary analyses using immunohistochemistry (43/45) or orcein staining (2/45) was performed to highlight vascular invasion. The CRM was analyzed in 87% of cases and was negative in 87% of cases (Table 1). The mesorectum was analyzed in 66% of cases and was complete or almost complete in 61% of cases. In patients who received neoadjuvant treatment, TRG was specified in 66% (404/617) of cases. The main classifications used were Dworak, Mandard, and Rodel TRG [17, 18].

Rectal specimens according to neoadjuvant treatment

Rectal specimens treated with surgery alone ($n = 326$) were compared to those treated by radiochemotherapy and surgery ($n = 617$); 40 were excluded because of missing information for neoadjuvant treatment. Group characteristics are presented in Table 1. After radiochemotherapy and surgery, there was a trend toward a lower rate of LNs analyzed compared to surgery alone: a median of 15 vs. 15 ($p = 0.036$) and a mean of 16 vs. 18 ($p = 0.004$), respectively (Table 1). The proportion of patients with ≥ 12 LNs analyzed did not differ significantly with or without radiochemotherapy (71% vs. 76%, respectively) ($p = 0.095$). The threshold of 12 was reached in 8 cases due to revision of the specimen in 4/25 after radiochemotherapy and 4/13 after surgery alone. The rate of VI (irrespective of its mural location) was lower after radiochemotherapy compared to surgery alone (28% vs. 33%, respectively) ($p = 0.030$). The rate of pT4a was also lower in patients that received radiochemotherapy (2% vs. 10%) ($p < 0.001$) (Table 1). Globally, fewer centers had ≥ 12 LNs (77% vs. 95%), VI ≥ 30% (32% vs. 54%), pT4a ≥ 10% (9% vs. 36%), and all indicators (0% vs. 18%) after radiochemotherapy than after surgery alone (Fig. 2b).

Rectal specimens: pT4a according to tumor location and treatment

The rate of pT4a decreased progressively from the high to the middle and low rectum (11%, 6%, and 0.5%, respectively) ($p < 0.001$) (Table 2). The rate of pT4a was lower after radiochemotherapy than after surgery alone, and the difference was significant for the middle (3.1 vs. 14.3%; $p = 0.002$) and low (3.8 vs. 0%; $p = 0.023$) regions (Table 2).

Discussion

At a national level and during routine practice, the quality of rectal cancer pathology reports and quality of surgery were good in 2016 in France due to the high rate of mesorectum and CRM analyzed (66% and 87%, respectively) and to the high frequency of complete or almost complete mesorectum and negative CRM (61% and 87%, respectively). Because French guidelines did not propose QI for colorectal cancer specimen, we also evaluated the quality of pathology reports according to British QI. In this field, two of the three QIs of British guidelines were respected, as shown by the median number of 15 LNs analyzed and 30% of VIs reported. The third indicator, pT4a, was found only in 4% of the rectal specimens and did not reach the recommended 10% level.

The number of LNs analyzed is essential because it is correlated with pN stage, a major prognostic factor in rectal cancer [19, 20]. According to international guidelines, at least 12 LNs per rectal specimen must be retrieved irrespective of treatment. In our study, the median number of LNs analyzed was 15 and 81% of centers reported ≥ 12 LNs. Our results are in accordance with a previous US population-based study that reported a median of 12 LNs in stage III rectal cancers [21]. However, a nationwide population-based study that focused on rectal cancer in the Netherlands reported a median number of only 7 LNs analyzed [22]. Neoadjuvant treatment, particularly long-course radiotherapy, decreases the number of LNs analyzed compared to untreated specimens [23, 24]. In our study, there was a trend toward a lower rate of LNs analyzed after radiochemotherapy, although the median number of LNs analyzed remained > 12 ($n = 15$). It is possible to increase the rate of LNs dissected using adjunct techniques (e.g., fat dissolution, compression or re-examination of specimens) [25, 26]. In our study, such techniques were rarely used, suggesting proper handling of rectal specimens.

The role of VI in rectal cancer is becoming increasingly important to consider in treatment decisions [9]. In our study, the rate of VI reached the threshold of 30% recommended by British guidelines. However, less than half of the centers (41%) reported ≥ 30% VI which is not satisfactory. Indeed, details of the structure involved and its mural location were lacking in most pathology reports. Obviously, French pathologists need to improve their VI detection sensibility. We recommend the following: (1) increase sampling in areas with linear spiculations at the advancing edge of the tumor [27];

Table 1 Main pathologic characteristics of the overall rectal cancer reports ($n = 983$) and comparison between rectal tumors treated by surgery alone versus surgery with neoadjuvant treatment ($n = 943$)

	Overall population		Surgery alone		Surgery and radiochemotherapy		*p*
	($n = 983$)		($n = 326$)		($n = 617$)		
	n	(%)	*n*	(%)	*n*	(%)	
Type of surgery							*< 0.001*
Specified	523	(53)	135	(41)	385	(62)	
Not specified	460	(47)	191	(59)	232	(38)	
Rectal location							*< 0.001*
Low	350	(35)	53	(16)	297	(48)	
Middle	262	(27)	70	(22)	192	(31)	
High	165	(17)	124	(38)	41	(7)	
Not specified	206	(21)	79	(24)	87	(14)	
Number of lymph nodes (LN) analyzed							
Median (IQR)	15 (11–21)		15 (12–23)		15 (11–20)		*0.036*
Mean ± SD	17 ± 9		18 ± 10		16 ± 9		*0.004*
Patients with ≥ 12 LN							
Yes	712	(72)	249	(76)	440	(71)	0.095
No	271	(28)	77	(24)	177	(29)	
Vascular invasion[a]							*0.030*
Yes	292	(30)	106	(33)	173	(28)	
No	655	(67)	215	(66)	416	(67)	
Not specified	36	(4)	5	(2)	28	(5)	
Perinervous invasion							0.089
Yes	221	(23)	71	(22)	141	(23)	
No	710	(72)	246	(76)	440	(71)	
Not specified	52	(5)	9	(3)	36	(6)	
Tumor budding							0.111
Yes	48	(5)	19	(6)	29	(5)	
No	75	(7)	18	(6)	57	(9)	
Not specified	860	(88)	289	(89)	531	(86)	
Tumor staging[b]							*< 0.001*
pT0	56	(6)	5	(2)	51	(8)	
pTis	17	(2)	11	(3)	6	(1)	
pT1	77	(8)	43	(13)	33	(5)	
pT2	253	(26)	82	(25)	162	(26)	
pT3	492	(50)	149	(46)	316	(51)	
pT4a	42	(4)	31	(10)	11	(2)	
pT4b	42	(4)	4	(1)	36	(6)	
Not specified	4	(0.4)	1	(0.3)	2	(0.3)	
Lymph node staging							0.741
pN0	627	(64)	213	(65)	393	(64)	
pN1	228	(23)	74	(23)	145	(24)	
pN2	125	(13)	39	(12)	77	(13)	
pNx	3	(0.3)	0	(0)	3	(0.3)	
Positive lymph nodes							
Median (IQR)	0 (0–1)		0 (0–1)		0 (0–1)		0.678
Mean ± SD	1.3 ± 3.1		1.4 ± 3.5		1.3 ± 2.8		0.703
CRM							*< 0.001*
Specified	855	(87)	252	(77)	571	(93)	

Table 1 (continued)

	Overall population		Surgery alone		Surgery and radiochemotherapy		*p*
	(*n* = 983)		(*n* = 326)		(*n* = 617)		
	n	(%)	*n*	(%)	*n*	(%)	
Not specified	128	(13)	74	(23)	46	(7)	
CRM							0.100
Safe	742	(87)	226	(90)	488	(86)	
Involved	113	(13)	26	(10)	83	(14)	
Plane of mesorectal excision							*< 0.001*
Complete—almost comp	595	(61)	164	(50)	418	(68)	
Incomplete	47	(5)	9	(3)	38	(6)	
Not specified	341	(35)	153	(47)	161	(26)	

CRM circumferential resection margin, *SD* standard deviation, *IQR* interquartile range, significant p-value is written in italic

[a] Intra- and/or extramural

[b] UICC classification, 7th edition (2009)

(2) become familiarized with specific signs of vascular invasion, such as "orphan arteriole" (i.e., tumor deposits adjacent to arterioles without any identifiable vein) and "protruding tong" (i.e., elongated tumor nodule extending into perirectal fat throughout the muscularis propria) [27]; and (3) use an elastic stain and/or an immunostain against the endothelium (CD31; D2–40 for lymphatics) [5, 6, 11]. The French recommendations could be updated and enriched by VI precisions including type of structure involved and mural location. After radiochemotherapy, the rate of VI was lower compared to surgery alone (28% vs. 33%, respectively), in accordance with the literature [5, 6, 28].

pT4a reflects the aggressiveness of the tumor against the peritoneum. It is a factor of bad prognosis associated with an increased risk for peritoneal metastasis and justifies postoperative chemotherapy. pT4a is more frequent in colon cancer than rectal cancer, because two thirds of the rectum (low and middle regions) are located below the peritoneal reflection. This is probably why the British pT4a threshold is lower for rectal cancer (≥ 10%) than for colon cancer (≥ 20%) [4]. In our study, the rate of pT4a was very low (4%) and the rate of centers that reported ≥ 10% pT4a was also exceptionally low (18%). At the end of 2017, pT4a was removed from the revised RCP recommendations as a QI for rectal cancer specifically [5, 6]. The reason advocated was the influence of radiochemotherapy. In this study, comparison of the rate of pT4a according to rectal location and treatment showed that not only treatment but also location modified the rate of pT4a. The threshold

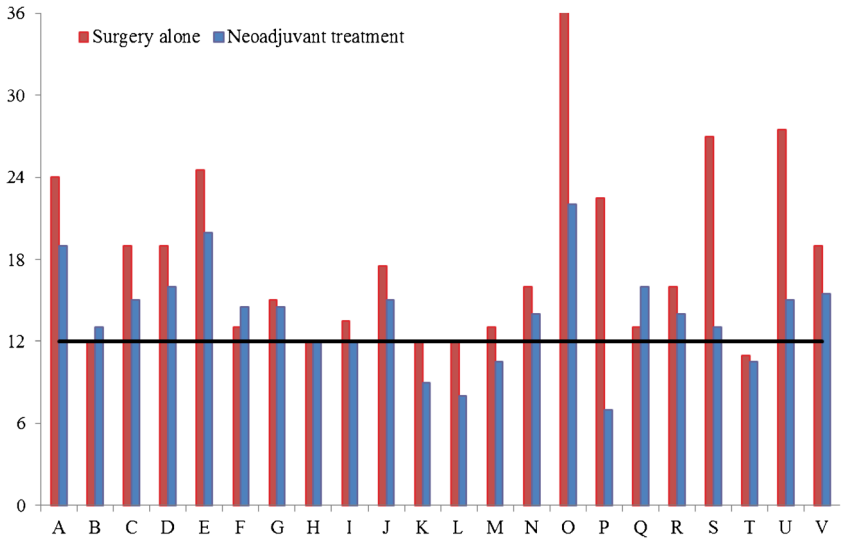

Fig. 1 Number of lymph nodes retrieved per center in rectal cancer reports in France (centers are classified according to decreasing number of cases in 2016)

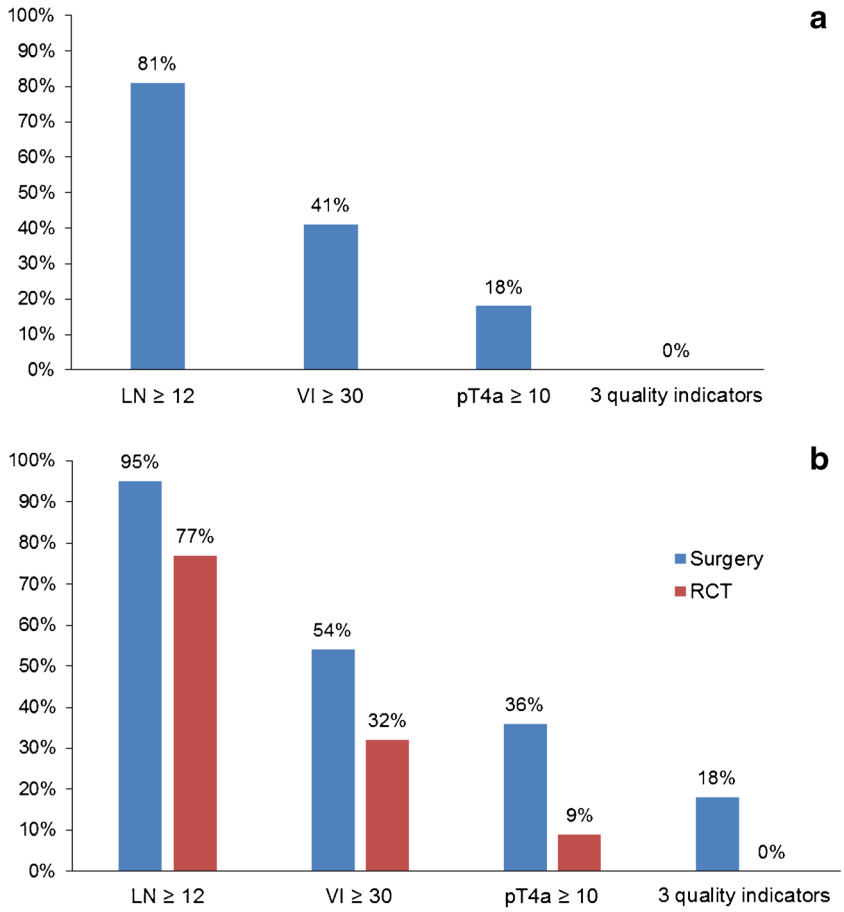

Fig. 2 Rate of French centers validating each quality indicator separately (LN: lymph node, VI: vascular invasion, pT4a: peritoneal invasion) and the three together (**a** overall rectal specimen; **b** rectal specimen according to neoadjuvant treatment)

of 10% was reached for high (irrespective of treatment) and untreated mid rectal cancers. Therefore, in the setting of rectal cancer reports, the relevance of pT4a as a QI is limited, particularly for mid and low (irrespective of treatment) rectal cancers. Therefore, it is necessary to identify a more specific indicator of rectal cancer specimens and reports.

The best candidate for a specific QI for pathology rectal cancer reports should be the CRM. Indeed, the CRM is already a QI for surgery and one of the main powerful prognostic factors in rectal cancer [29]. In our study, the rate of CRM analyzed and safe was very high, higher than some randomized rectal cancer trials [30], suggesting careful pathology analyses in routine practice in France. One bias of this result could reside in the recruitment of pathology laboratories; most were enrolled in the French clinical trials of rectal cancer (GRECCAR group) [14].

In conclusion, in French routine practice, two of the three QIs (LNs analyzed and VI) were globally in line with RCP guidelines for rectal cancer reports. However, effort is needed to improve the detection and characterization of VIs. Regarding pT4a, the third and most controversial QI, the rate was very low, particularly in subperitoneal rectal cancer and after radiochemotherapy. A more specific and relevant indicator for rectal cancer, such as the CRM, should replace pT4a in the evaluation of rectal cancer report quality.

Table 2 Rate of pT4a according to rectal location and treatment

	Overall population *n* (%)	Surgery alone *n* (%)	Surgery and radiochemotherapy *n* (%)	p^a
Low	2/350 (0.5)	2/53 (3.8)	0/297 (0.0)	*0.023*
Mid	16/262 (6)	10/70 (14.3)	6/192 (3.1)	*0.002*
High	18/164 (11)	14/123 (11.4)	4/41 (9.8)	1.000

[a] Modified χ^2 test, significant p-value are written in italic

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Compliance with ethical standards

In this work, all pathology reports were anonymized before analysis. Therefore, no informed consent was obtained.

Conflict of interest The authors declare that they have no conflicts of interest.

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