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The impact of EUS to predict lymph node metastasis in patients with rectal cancer: a difficult challenge

A. VANNELLI[1], E. POIASINA[2], L. BATTAGLIA[3]

[1]Unit of Surgical Oncology, Ospedale Valduce, Como, Italy
[2]Division of General Surgery, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[3]Unit of Colo-rectal Surgery, Foundation IRCCS "Istituto Nazionale dei Tumori", Milan, Italy

Abstract. – OBJECTIVE: Current trends in the management of rectal cancer, identify accurate local assessment of positive lymph nodes (LN), as the strongest predictor for stratifying patients who would benefit from preoperative therapy. We a present retrospective analysis of a prospective data collection, to determine the clinical concordance between the suspicious LN at the pre-operative EUS (uN) and a post-operative EUS detection (pN).

PATIENTS AND METHODS: From March 2009 to March 2011, 31 patients with suspicious LNs at EUS (uN positive) were enrolled. The surgeon performed pre-operative EUS and directly in the operating room, an *ex vivo* EUS of the specimen. The immediate mesorectal LN sampling by the surgeon was delivered to the pathologist. Endosonographic staging was compared to postoperative pathological staging.

RESULTS: Preoperative EUS identified 67 suspicious LN. The LN medium size was 6.8 mm. We repeated the EUS after surgery. The pathologist found 41 positive LN. The definitive LN medium size was 6.3 mm. Eleven LN presented the same size between ultrasound and pathological examination, 11 LN a smaller size and 41 a bigger size, the remnants 4 were not discovered. EUS LN staging presented 83.9% in overstaging and 3.2% in understaging. Although endo ultrasonography (EUS) is a very effective method for assessing LN metastasis, this is still a difficult challenge. Inaccurate assessment of LNs can conceivably lead to either under-staging or overstaging. The present study indicates that the clinical concordance between the suspected metastatic LN at the pre-operative EUS (uN) and a post-operative (*ex-vivo*) ultrasound LN detection, is moderate.

CONCLUSIONS: We should re-consider all this strategy: we need to switch from morphological information to biological behavior.

Key Words:
Lymph node, Endo ultrasonography, Rectal cancer, Staging accurancy.

Introduction

Over the last thirty years, there has been a marked variability in the management of rectal cancer from the total mesorectal excision (TME), to the role of preoperative therapy, and, finally, to the correlation between resection margin and local recurrence[1-3]. All together, these approaches, have improved outcomes worldwide[4].

The current trends in management of rectal cancer, identify accurate preoperative staging as the strongest predictor for recurrence[5]. Accurate local assessment is necessary for stratifying patients who would benefits from preoperative therapy as well as for predicting the surgical approach. Today, as reminded by Minsky[6]: "the most pressing question is not whether preoperative therapy is preferred, it is how to identify more accurately patients with positive lymph nodes (LN), so they can be treated with preoperative chemoradiotherapy".

Morphologically, quantitative measurements of suspicious LN, is well recognized as one of the most important prognostic factors for choosing therapeutic treatment and an overall long-term outcome. Although reliable preoperative imaging evaluation is vital to surgical planning the majority of patients with rectal cancer still received inadequate LN evaluation[7,8]. The reasons for this inadeguacy are that some enlarged palpable LNs contain metastases, the presence of reactive inflammatory nodes is frequently observed, and approximately 18% of LNs with metastatic foci are < 5 mm in diameter[9-12].

Nowadays, several modalities exist for the assess preoperative LNs staging: Endo ultrasonography (EUS), magnetic resonance (MRI), computed tomography (CT) and positron emission tomography (PET). EUS and MRI are the best available modality for local staging of rec-

Corresponding Author: Alberto Vannelli, MD; e-mail: info@albertovannelli.it

tal cancers, and play an important role in accurately distinguishing which patients should receive preoperative chemoradiation. Alternatively, both CT and PET are considered primary modalities when performing preoperative distant staging, but are limited in their ability to locally stage rectal malignancies[13]. Typically, a combination of these approaches is used to provide complete morphological information, but which technique is utilized is often influenced by local expertise and technological accessability. Despite recent progress, the criteria used to define the suspicion of disease are still anchored in an old model of morphological analysis. LNs staging refers to the pioneering study of Hildebrandt et al[14] which described the identification of suspicion of disease on positive LNs, through EUS, and revolutionized the history of rectal cancer staging. However, the current policy has remained unchanged: today the impact of EUS to predict LN metastasis in patients with rectal cancer, is a still a difficult challenge[9]. Perhaps, taking each approach one step at a time and following in the Hildebrandt and Fiefel's footsteps[15] on *in vivo* evaluation would help find a better solution for the management of rectal cancer.

The aim of this retrospective analysis, based on a prospective data collection, is to establish the impact of EUS to better predict LN metastasis in patients with rectal cancer and without preoperative therapy. Moreover, by utilizing pathologic staging as the gold standard it would be possible to determine the clinical concordance between the suspicious LN at the pre-operative EUS (uN) and a post-operative EUS detection (pN).

Patients and Methods

All patients admitted to the Unit of Colo-rectal Surgery at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan, from March 2009 to March 2011, with the diagnosis of rectal adenocarcinoma, were prospectively considered. All patients were locally examined preoperatively with EUS and MRI for staging (uT/uN), according to "Rete Oncologica Lombarda" (ROL) Clinical Practice Guidelines for Rectal Cancer[16]. Moreover, we considered the rectum cut-off within 15 cm from the anal verge and intra-peritoneal cut-off more than 12 cm from the anal verge. The inclusion criteria for this study was limited to a not stenotic and extraperitoneal rectal adenocarcinoma with preoperative mesorectal positive LNs unfit to preoperative therapy. On the other hand, patients admitted with previous preoperative treatment (radio and chemotherapy), and/or with loco-regional recurrence, and/or previous pelvic surgery and/or with more than one primary cancer, were excluded from this study. Also patients with positive LNs who received preoperative therapy were not considered. Overall, thirty-one patients with suspicious LNs at the EUS and MRI (uN positive) were enrolled. Approval by the institutional Review Board and an informed consent specifying the use of biological samples for research purposes were obtained.

The status of LN was carefully evaluated for each patient through three steps. The first step was a cleansing of the rectum by 2 disposable enemas (Fleet; Merck & Co, Whitehouse Station, NJ, USA), immediately before the study. In details, the EUS was performed with the patient positioned in left lateral decubitus, in the knee-chest position. Optimal imaging requires adequate patient preparation and meticulous technique, therefore before inserting the ultrasound probe into the rectum, a digital rectal examination was performed to identify the location, size, morphology and motility of the tumor. EUS was performed by using a rotating scanner (Hitachi H19-H20s, Tokyo, Japan) with a resolution of < 1 mm. The rectal probe, 16 cm in length with a head diameter of 21 mm, was utilized and EUS was performed by introducing a water-filled balloon containing the high-frequency transducer and trans-anal probe into the rectum. This way it was possible to better delineate the five layers of the rectal wall, as alternating hyper-echoic and hypo-echoic bands. Moreover, during the examination it was possible to regulate the frequency from 7.5 MHz to 5 MHz with a maximum tissue penetration of approximately 7 cm for the latter one. Finally, the transducer is able to rotate at a speed of 12 cycles per second generating a 360° real-time image. All examination were performed by experienced and trained surgeons, who participated in EUS training with supervision. Round, hypoechoic LN and larger than 5 mm, according to ultrasonographic criteria, were deemed malignant[15]. The surgeon identified all the suspected metastatic LN at the preoperative EUS: uN positive (Figure 1), whereas the number, size, and position of uN positive were recorded on a database. This made it possible to map the mesorectum.

Figure 1. Round hypo echoic lymph node with smooth and sharply defined borders (D1: 7.2 mm).

The second step was the anterior resection of the rectum (ARR), by the surgeon, with total mesorectal excision (TME), as previously described[17]. This technique involves dissection in the areolar plane between the fascia propria (visceral fascia) of the rectum and the parietal pelvic fascia. For upper rectal tumors, the rectum and mesorectum were divided 5 cm distal to the caudal tumor edge. For tumors of the mid and distal rectum, a TME was performed. In the operating room, the same surgeon performed an *ex vivo* EUS of the specimen, in order to update the database with number, size, and position of LN (*ex vivo* LN positive). The previous LN map was compared with the newly ones here obtained using the same machine. This allowed us to recognise the previous suspicious uN positive (Figure 2).

Figure 2. The surgeon perfomed EUS of the specimen of the rectum after surgical resection (*ex vivo*).

The third and final step was performed by the surgeon who marked the suspicious pathological mesorectal nodes (previous uN positive, now *ex vivo* LN positive) with a stitch. At the time of mesorectal LN sampling by the surgeon was immediately delivered to the pathologist (Figure 3). All the pathologist's reports from ARR specimens, were examined prospectively, by a single specialized pathologist in our department of pathology. All LNs were delivered in the fresh state and immediately used haematoxylin-eosin staining to detect cancer cell: pN. For each report, the total number of LNs and the method of identifying LNs was recorded. LNs were identified according to the UICC TNM anatomical groupings.

Statistical Analysis

A descriptive analysis of the test performance of suspected metastatic LN at preoperative EUS (uN) and post-operative (*ex-vivo*) EUS (pN) was carried out with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

A total of 281 consecutive patients affected with rectal cancer were submitted to surgical treatment from March 2009 to March 2011, at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan. Overall, only 31 patients where unfit to preoperative therapy (19 males and 12 females), and were, therefore, enrolled in the present study. The mean age was 62.6 (range 47-77).

Preoperative EUS identified 17 patients (54.8%) with T2 stage, 13 (41.9%) with T3 stage and 1 (0.3%) with T4 stage (Table I). All patients presented suspected metastatic LN: uN positive, we globally registered 67 LN; more than 2 LN for patient (range 1-3). The LN medium size was 6,8 mm (range 3.2-20; DS 3.4). Briefly, 40 LN were placed around to the tumor (3 antero-lateral to left, 3 lateral to left, 19 postero-lateral to left, 6 posterior, 9 postero-lateral), 24 LN over the tumor and 3 LN under the tumor. After ARR with TME, we repeated the EUS. We discovered 63 LN: in 4 patients the specimen was manipulated during the resection and the previous map of the mesorectum changed, so four LN were not identified.

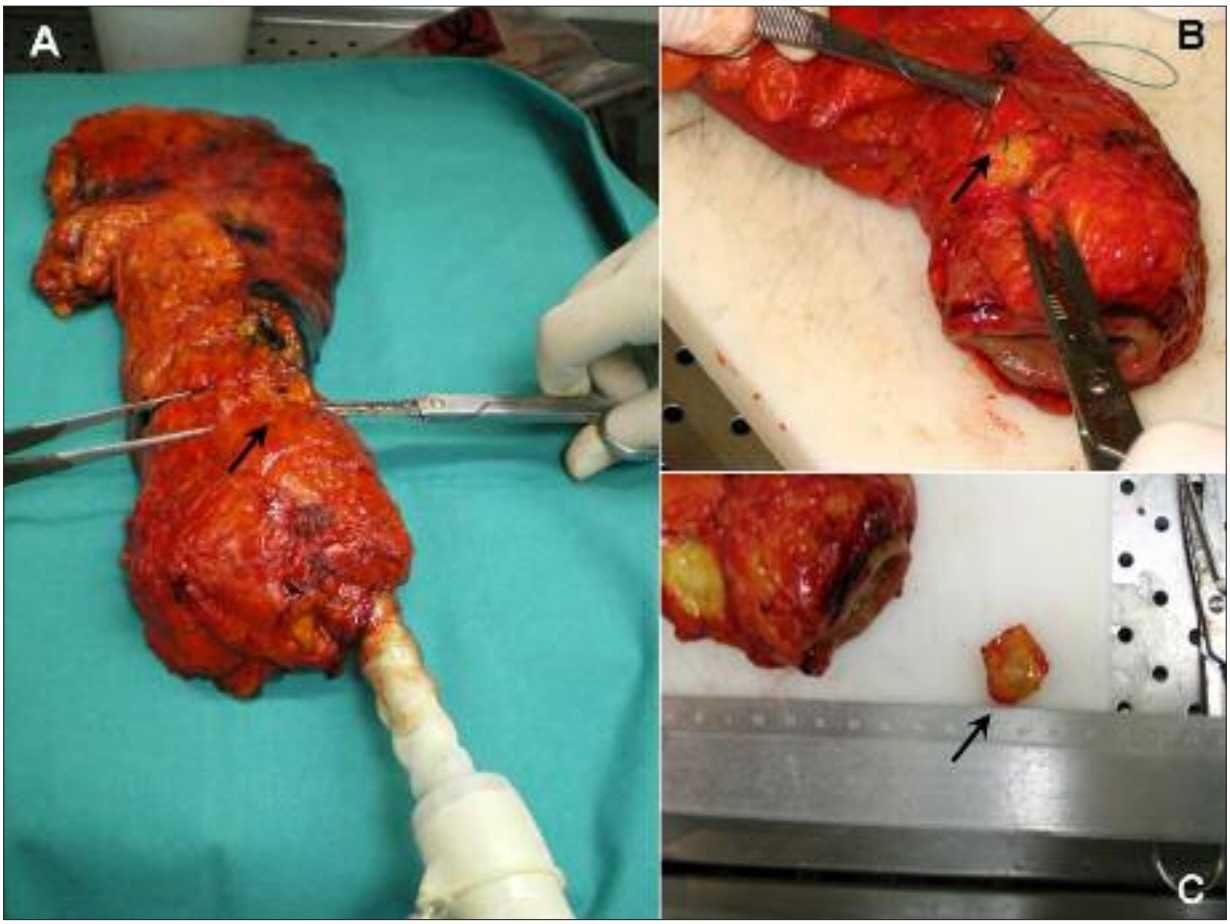

Figure 3. ***A,*** Suspicious LNs: previous uN positive, now ex vivo LN positive (*black arrow*). ***B,*** The surgeon marked *ex vivo* LN positive with a stitch (*black arrow*). ***C,*** The immediate mesorectal LN sampling by the surgeon was delivered to the pathologist (*black arrow*).

Pathological examination documented 12 patients (10%) with T2 stage, 11 (70%) with T3 stage and 1 (20%) with T4 stage; 13 patients (41.9%) had positive lymph nodes. EUS T staging presented: 0% in overstaging and 6.5% in understaging (Table I). Pathologist's review identified 772 LN (range 14-43): a median of 24.9 nodes each patients (DS 8.5), LN positive were 41: a median of 1,3 node each patient (DS 2.5). The definitive LN medium size was 6,3 mm (range 3-20; DS 3.2). EUS detected a mean of 2.2 nodes/patient, with a diameter ranged from 3.2 mm to 20 mm (mean 7.3 mm). Moreover, 11 LN presented the same size between ultrasound and pathological

Table I. Comparison between tumor EUS, and pathologic stage of rectal cancer.

EUS stage	Total	Pathologic stage			Overstaging	Understaging
		pT2	pT3	pT4		
uT2	17	17	0	0	0%	0%
uT3	13	2	11	0	0%	15.4%
uT4	1	0	0	1	0%	0%
Total	**31**	**18**	**11**	**2**	**0%**	**6.5%**

Stage represents: T2 tumors confined to the rectal wall, T3 tumors penetrating the rectal wall and invading perirectal fat, T4 tumors invading adjacent organs.

Table II. The effect of adoptive transfer of MDSCs on airway responsiveness.

EUS stage	Total	Pathologic stage			Overstaging	Understaging
		pN0	pN1	pN2		
uN0	0	0	0	0	0%	0%
uN1	19	15	3	1	78.9%	5.2%
uN2	12	3	8	1	91.6%	0%
Total	**31**	**18**	**11**	**2**	**83.9%**	**3.2%**

Stage represents: N0 no regional metastatic nodes, N1 < 3 malignant perirectal lymph nodes, N2 > 3 malignant perirectal lymph nodes.

examination, 11 LN a smaller size and 41 a bigger size, the remnants 4 were not discovered. EUS LN staging presented 83.9% in overstaging and 3.2% in understaging (Table II). All patients with pT3/4 and pN-positive received post-operative treatment (radio plus chemotherapy).

In our clinical series, the median duration of follow-up was 68.2 (range 75-65) months. The 5-year overall survival and disease free suvival for the 31 patients with rectal cancer were: 70.1% and 40.9%, respectively (Table III). The 5-year local recurrence free survival and distant metastasis free survival were 94% and 71%, respectively. The follow-up showed 3 local recurrence after 28, 30 and 39 months (one patient lived after total pelvic exenteration for pelvic recurrence), 11 liver metastases after a mean of 34.8 months (survival: 6 patients), 5 lung metastases after a mean of 29.5 months (survival: 2 patients) and one brain metastasis after 42 months (dead 6 months after the diagnosis).

Discussion

Accurate preoperative staging is the strongest predictor for rectal cancer recurrence[5], and these information are critical for identifying patients who would benefits from preoperative therapy as well as for choosing the most appropriate surgical approach[18,19]. Unfortunately, it is only possible to accurately stage the malignancy with histological examination of the LNs after resection, and preoperative assessment in rectal cancer still remains a complicated challenge. Following the pioneering study of Hildebrandt and Fiefel, literature lacks of proper radiological criteria for LN metastatic involvement in the mesorectum and pelvis[15].

In our study, we attempted to investigate the predictive value of morphologic concordance with EUS. The local staging work-up consists of EUS and/or MRI. Our study demonstrated that all LNs may not be visible in physiological conditions using EUS and other radiological procedures, and our data shows that the probability of metastases is high in LN smaller than 5 mm: 40%.

Identification of involved LN located outside of the mesorectal fascia is important, as they will not be removed during a standard ARR with TME. Such nodes may require additional treatment since they are responsible for local recurrence. This correlation depends on the ab-

Table III. Patient details.

pTNM	Patients	Recurrence	Metastasis	Survival
Stage I	13 (41.9%)	0	1 (lung)	13 (100%)
Stage IIa	2 (6.5%)	0	1 (liver)	2 (100%)
Stage IIb	None	None	None	None
Stage IIc	1 (3.2%)	1	0	1 (100%)
Stage IIIa	5 (16.1%)	0	5 (3 lungs, 2 livers)	3 (60%)
Stage IIIb	5 (16.1%)	0	5 (4 livers, 1 brain)	2 (40%)
Stage IIIc	3 (9.7%)	2	3 (liver)	1 (33.3%)
Stage IVa	2 (6.5%)	0	2 (1 lung, 1 liver)	0 (0%)
Stage IVb	None	None	None	None

sence of nodes with mixed echo patterns, otherwise they cannot be accurately classified and should be estimated as metastatic. In our study we did not find any suspected positive LN in lateral regions. Presently, a combination of several modalities is used to provide complete information for the preoperative LNs staging of rectal cancer and the choice is often influenced by institutional protocols and their accessibility to technologies.

Scientific evidence for a preoperative pathological LN, however, is questionable and the use of universal cut off values should be re-considered. Debate exists regarding the importance of preoperative LN imaging with a rationale to "improve" staging. The role of EUS for the staging of rectal cancers LNs is widely accepted in all Clinical Practice Guidelines[20-22]. On the other hand, EUS hasn't proved to be one of the best means of assessing neoplastic infiltration and therefore it should not be useful in a morphologic analysis as prediction of regional LN status in rectal cancer. For a long time, the morphologic criteria were: the lack of an oval shape and fatty sinus, round or irregular margin, as well as short transversal diameter over 10 mm. However, by using such criteria, the reported accuracy was relatively low. In our study, EUS stage showed a positive uN1 and uN2 of 61% and 39% respectively but after pathological evaluation the rate of positive LN changed: 9% and 29% respectively. Moreover, uN2 showed a 9.7% of negative LN, after pathological evaluation (pN0).

Currently, there is a tendency to report any pelvic LNs, since their transversal diameters and their implications have not been established in any large and multicenter studies[23]. The irregular borders and signal intensity are principle features in node metastasis, according to the European Registration of Cancer Care (EURECCA) algorithm: nodes > 3 mm can be characterized as malignant or benign by signal and border features[24]. In our study the mean size of LN was 6.6 mm (DS 1.8); the mean size of pN positive was 6.14 mm (DS 1.9), on the contrary the mean size of pN negative was 6.51 mm (DS 1.8). Based on new clinical observations, a well-preformed TME, limiting nodal involvement, is no longer a risk factor for a local recurrence.

EUS and MRI are adequate and comparable techniques for T and N staging of colorectal cancer. However, unlike MRI, EUS is influenced by tumor stenosis, not allowing exclusion of distant metastasis, and is unable to identify the mesorectal fascia, which is crucial for predicting tumoral involvement of the circumferential resection margin.

Inaccurate assessment of LNs can conceivably lead to either under-staging with an increased risk of local recurrence, or over-staging with unnecessary preoperative treatment, and important functional consequences[25]. In our study a lot of patients (41.9%) presented low risk according with pTNM classification, but preoperative staging (EUS plus RMN) suspected a great number of LN involved; all patients with stages III and IV, according with pTNM classification, received post operative treatment and the follow-up, showed only 3 local recurrence (Table III).

The present study indicates that the clinical concordance between the suspected metastatic LN at the pre-operative EUS (uN) and a post-operative (*ex-vivo*) EUS LN detection, is moderate and therefore the strategy should be reconsidered. The need to switch from morphological information to biological behavior should be essential. Many authors yet utilize bioinformatics analysis to explore the function of prognostic biomarkers for patients with rectal cancer[26]. Moreover recent studies suggest that young patients with rectal cancer have distinct clinicpathological and molecular entities compared to elderly patients[27]. Although radiotherapy together with surgery have improved the survival, there is still a large proportion of patients receiving RT without any benefits, but experiencing side effects. Advances in molecular biology have provided an opportunity to select patients suited for therapy and determine prognosis[26]. Functional imaging techniques give more comprehensive information on tumor morphology and underlying tissue characteristics. Some of these imaging biomarkers, have already been implemented into clinical protocols, others are still under investigation. Multiparametric imaging in rectal cancer patients will significantly improve the radiologist's performance, in particular for treatment response evaluation[28,29]. Apart from that, technical developments in MR scanner hardware, the clinical introduction of hybrid PET–MR scanners, the influence of post-transcriptional regulation of mRNA in assessing the LN status, and LNs sampled by endoscopic ultrasound fine-needle aspiration, are the beginning of a new era[30-32].

While Minsky[33] wrote: "The therapy of rectal cancer continues to evolve. Both diagnostic and therapeutic advances are challenging historical

approaches and have opened new directions for the future and are areas of clinical investigation", the american author on motivation, Brendon Buschard[34], said: "Challenge is the pathway to engagement and progress in our lives". The name of this challenge is the investigation of biological discoveries in LNs metastases. J.J. Keynes[35] said: "The difficulty lies not so much in developing new ideas as in escaping from old ones".

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Conflict of Interest

Authors disclose no commercial or other associations that might pose a conflict of interest in connection with submitted material.

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