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Colorectal cancer and lymph nodes: The obsession with the number 12

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Abstract

Lymphadenectomy of colorectal cancer is a decisive factor for the prognostic and therapeutic staging of the patient. For over 15 years, we have asked ourselves if the minimum number of 12 examined lymph nodes (LNs) was sufficient for the prevention of understaging. The debate is certainly still open if we consider that a limit of 12 LNs is still not the gold standard mainly because the research methodology of the first studies has been criticized. Moreover many authors report that to date both in the United States and Europe the number "12" target is uncommon, not adequate, or accessible only in highly specialised centres. It should however be noted that both the pressing nature of the debate and the dissemination of guidelines have been responsible for a trend that has allowed for a general increase in the number of LNs examined. There are different variables that can affect the retrieval of LNs. Some, like the surgeon, the surgery, and the pathology exam, are without question modifiable; however, other both patient and disease-related variables are non-modifiable and pose the question of whether the minimum num-

ber of examined LNs must be individually assigned. The lymph nodal ratio, the sentinel LNs and the study of the biological aspects of the tumor could find valid application in this field in the near future.

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Key words: Colorectal cancer; Lymphadenectomy; Lymph node count; Lymph node ratio; Staging

Core tip: Lymphadenectomy of colorectal cancer is a decisive factor for the prognostic staging of the patient. A limit of 12 lymph nodes (LNs) is still not the gold standard and accessible only in highly specialized centers. There are different variables that can affect the retrieval of LNs; some are non-modifiable and pose the question of whether the minimum number of examined LNs must be individually assigned.

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INTRODUCTION

In 1998, Curti *et al*^[1] stressed that continually talking about the lymphadenectomy of colorectal cancer makes for incredibly monotonous reading. In fact, even though it has been proven that the excision of lymph nodes (LNs) in colorectal cancer is a crucial measure, in the last decade the problem has mainly shifted its focus to the physical dimensions of the lymph nodal excision and, more specifically, to the number of LNs to be removed. Even if in this area there are precise indications, in reality, they

are not always respected due to, above all else, the large number of variables that can interfere with the sampling of the LNs.

MEANING OF LYMPHADENECTOMY

All histological staging, even the recent seventh edition of the AJCC^[2], has considered the metastatic involvement of the LNs a determining factor for the staging of the colorectal tumor^[3-28] as long as examined in sufficient numbers to ensure the “certainty” of a patient’s prognostic classification^[13]. Actually, this is not the case, since as we shall see, the lack of reliable data makes the current staging systems inadequate. This lack creates episodes of “stage migration,” which are likely responsible for the 20%-25% of the cases in which a node-negative patient relapses^[29-34], as well as for better prognoses for patients staged IIIa than for those staged IIb^[31-34].

The correct staging of a patient treated for colorectal cancer is also critical in the planning of adjuvant therapies that certainly, especially for stage III, ensure improved outcomes and may not be prescribed to a patient who has a falsely-judged more “favorable” staging^[3,8,10,11,15,17,19,22-24,27,31,33,35-37]. In this context, some authors as well as some organizations such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend adjuvant chemotherapy to patients for whom the LN study proved insufficient^[7,21,25,35,38,39].

In addition to its accuracy in staging, the LNs excision also seems to be an independent prognostic factor. Many case-study reviews^[3-5,10,11,14,19,20,24-28,35,40-49], particularly in patients with stage II, report a directly proportional relationship between the number of LNs removed and survival. In this regard, it seems appropriate here to refer to the systematic review of Chang *et al.*^[24] who report that in 16 of 17 studies the increased survival of patients with stage II colon cancer was associated with increased numbers of LNs evaluated. The most likely explanation is that the higher the number of LNs examined the better select the group of node-negative patients with a better prognosis for which surgery alone should be curative. Other authors^[1,21,40,50], however, believe that in patients with more advanced stages, the lymphadenectomy can be therapeutic both by improving tumor clearance by the surgeon and by reducing the metastatic spread through lymphatic drainage. Not all authors agree with this latter view^[5,11].

Last but not least, it must be noted that organizations such as the American College of Surgeons, the ASCO, and the National Quality Forum consider the entity of the lymphadenectomy as a way to gauge the quality of a center dealing with this type of pathology^[51-55]. Concerning this issue, not all are in agreement mainly because the number of LNs removed may not reflect the quality of the surgeon or the pathologist but, as we shall see later, may be tied to unchangeable factors inherent in the patient or the tumor^[6,50].

NUMBER OF LNs NECESSARY FOR A CORRECT STAGING

Many authors^[17,27,28,56] claim that in clinical practice there should be no set limit to the number of LNs examined since in addition to survival, as has already been mentioned, there is a direct correlation between the number of examined LNs and the number of LNs with metastasis^[4,14,24,28, 57-59].

However, in light of this observation, we have to ask ourselves what the minimum number of LNs is, beyond which there is no change in the staging if not within acceptable limits. Therefore, along with McDonald *et al.*^[6] we believe that a “ceiling effect may be reached”, above all for the purposes of allowing pathologists to realize the point at which they can feel satisfied with their search no matter how many LNs may be left in the piece removed. In fact, there is no doubt that in the “real world”, pathologists, with the methods that are presently available, do not or simply cannot sample all removed LNs especially when they are small^[15].

In light of this, the number of LNs to be sampled still varies widely even though it has been discussed for over 20 years. In fact, since 1990, at the World Congress of Gastroenterology in Sydney, 12 was established as the minimum standard of LNs to be examined since this number would allow for a correct diagnosis of N0 in 90% of cases^[6,21,51,60].

This number, referred to as “magic”^[50], was later included in many guidelines and has been endorsed by a large number of United States and European organizations^[7,9,17-19,36,40, 50,51,61,62].

In this regard, what Stocchi *et al.*^[41] have recently reported seems paradigmatic. He claims that, considering only patients treated for stage II colon cancer, the examination of at least 12 LNs is associated with an improvement in results; this improvement reduces if a smaller sample of LNs get examined, but it does not increase with a larger sample of LNs.

Other data reported by Nelson *et al.*^[51], Norwood *et al.*^[19], and Lee *et al.*^[58] show data compatible with Stocchi’s theory. Nelson *et al.*^[51] report that by examining 12 LNs, the lymph nodal positivity is correctly identified in 90% of patients; Norwood *et al.*^[19] claim that only when the number of LNs is < 12 there is a reduction in the survival rate; finally, Lee *et al.*^[58] reports that the examination of a number of LNs ≥ 12 increases the chance of diagnosing positive LNs by 30%.

In light of this data, the number 12 indeed seems correct, but this is not the case of course if in 2012 Fingerhut^[4] still asked himself, “Why all the fuss?”

The debate is certainly still open if we consider that a limit of 12 LNs is, as of today, still not the gold standard mainly because the research methodology of the first studies^[40,63,64], which do not go beyond a level of III or IV and a grade C recommendation, has been criticized^[6,51].

In fact, in the literature there is no uniformity in determining what the minimum lymph nodal sampling is to allow for a greater diagnosis of positive LNs, a different

Table 1 Minimum lymph node sampling recommended for a correct staging

Under 12 LNs	LNs At least 12 LNs		LNs Over 12 LNs	LNs	
	<i>n</i>	<i>n</i>			
Caplin <i>et al</i> ^[65]	7	Nir <i>et al</i> ^[18]	12	Swanson <i>et al</i> ^[57]	13
Maurel <i>et al</i> ^[66]	8	Norwood <i>et al</i> ^[119]	12	Wong <i>et al</i> ^[71]	14
Mekenkamp <i>et al</i> ^[67]	8	Stocchi <i>et al</i> ^[41]	12	Tepper <i>et al</i> ^[72]	14
Yoshimatsu <i>et al</i> ^[26]	9	Wong <i>et al</i> ^[46]	12	Wong <i>et al</i> ^[73]	14
Sarli <i>et al</i> ^[35]	9	Kukreja <i>et al</i> ^[50]	12	Chen <i>et al</i> ^[48]	15
Cianchi <i>et al</i> ^[68]	9	Nelson <i>et al</i> ^[51]	12	Mukai <i>et al</i> ^[74]	15
		Lee <i>et al</i> ^[58]	12	Goldstein <i>et al</i> ^[75]	17
		Bilimoria <i>et al</i> ^[69]	12	Tsai <i>et al</i> ^[25]	18
		Storli <i>et al</i> ^[70]	12	Le Voyer <i>et al</i> ^[27]	20
				Joseph <i>et al</i> ^[76]	30
				03 (T3)	
				Joseph <i>et al</i> ^[76]	40
				03 (T4)	

LN: Lymph node.

staging that justifies adjuvant chemotherapies, or, ultimately, a better survival rate (Table 1).

This confusion is also documented by McDonald *et al*^[6] who, citing 10 observational studies that analyzed more than 43000 patients, points out that not only is there no agreement on what the LN cut-off point should be, but that in a wide range of LNs examined (between 6 and 21) the actual cut-off point fluctuated. This range is similar to the one reported by Valsecchi *et al*^[21] (between 6 and 17) and lower than the one reported by Noura *et al*^[42] (between 6 and 40).

This variety of data leads us to ask what our main objective is when we examine LNs? If the goal is to “certify” a node-negative patient, then evaluating a number of LNs equal to 12 or perhaps even higher is likely to be necessary; if instead metastatic LNs are identified, it is then possible to “settle” for a smaller number of LNs which, according to some authors^[46], are easier to identify as they are more visible and palpable. However, even in this respect “everything and the opposite of everything” can be said if considering what is reported by some authors^[35,60,77] who claim that about 50% of enlarged LNs are negative or only an expression of a vigorous immune response, while 45%-78% of metastatic LNs have a less than 5 mm diameter.

Gelos *et al*^[78], however, focus on yet another aspect, arguing that in patients with a malignancy at an earlier stage which can lead to a lower immune response, it is likely that we can settle for a sample of less than 12 LNs.

The fact that even today the number “12” target is “uncommon, “not adequate,” or accessible only in highly specialized centers^[21,41,50] is demonstrated by the fact that in the United States in 2001^[4], the number of 12 sampled LNs was reached for only 44% of patients and that the target of patients increased to 75% in only 38% of hospitals in 2004-05^[69], 15 years after Sydney. Moreover, once again in the United States, reports published between 2005 and 2010 revealed that, despite the “dense forest of articles”^[79] lymphadenectomy was still considered inad-

Table 2 What “could interfere” with the lymph node count

Modifiable factors	Surgeons	Pathologist
	Specialization	Lack of training
	Case volume	Lack of time
	Surgical technique	Techniques
	Emergency	
	Extension	
	Laparoscopy	
Unmodifiable factors	Patient related	Disease related
	Advanced age	Tumor site
	Female	Tumor staging
	Obesity	Pre-operative radiotherapy

equate in 48% to 63% of cases^[79,80].

Similar experiences are also reported in Europe; in fact, in Germany in 2009, the Dutch Surgical Colorectal Audit^[77] reported that in 73% of colon cancers and 58% of rectum cancers, the number of LNs examined was ≤ 10; in England, Johnson *et al*^[81] and Mitchell *et al*^[82] have recently pointed out that the limit of 12 LNs was not reached between 33% and 50% of colorectal cancer cases.

It should however be noted that both the pressing nature of the debate and the dissemination of guidelines have been responsible for a trend that, over the years, has allowed for a general increase in the number of LNs examined, thus enabling the U.S. to increase the number of hospitals that reach the target of 12 LNs from 15% in 1995-96 to 38% in 2004-05^[69] and in 2005-2008^[52] reach the figure of 92% albeit only in centers that are members of the NCCN and are thus made up of top institutions^[69]. This, however, is probably not the case in smaller hospitals^[9,21].

WHAT CAN INTERFERE WITH LYMPH NODAL COUNT

Ideally, the surgeon should remove all the LNs pertaining to the tumor and the pathologist should sample and examine them thoroughly. However, even if this were carried out, all authors agree that there would be “unmodifiable” factors patient-related and disease-related that could make a node-count problematic (Table 2).

In our opinion, all the variables, modifiable and unmodifiable, that can affect lymph nodal sampling should be examined so as to make the work of both the surgeon and of the pathologist more efficient.

Modifiable factors

Surgeons and surgery: The extent to which a surgeon’s experience, specialization and case volume impact the quality of a performed surgery has often been considered a possible factor which can affect the number of removed LNs^[3,11,21,23,41,83] (Table 3).

Even if this seems logical^[35], if we consider Table 3 we can see that although the “surgeon variable” is considered an “independent factor”, there is no clear differ-

Table 3 Surgeon's experience vs lymph nodes harvested

Surgeon's experience		Statistical analysis	LN harvested (expert vs no expert)
Leung <i>et al</i> ^[11]	> 15 yr	MA: se independent factor ($P < 0.05$)	13 vs 11 LN
Valsecchi <i>et al</i> ^[21]	5 colon/yr	MA: se significant predictor ($P = 0.001$)	Not specified
Shaw <i>et al</i> ^[23]	Colorectal surgeon	UA: se $P = 0.002$	11 vs 9 LN
Stocchi <i>et al</i> ^[41]	Largest case volume	MA: se independent variable ($P = 0.018$)	86% vs 83.6% pts with ≥ 12 LN

MA: Multivariate analysis; UA: Univariate analysis; LNs: Lymph nodes; se: Surgeon's experience.

Table 4 Lymph node sampling in laparoscopic vs open approaches

	Laparoscopy		Open	
	Patients	LNs	Patients	LNs
	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>
COST ^[91]	435	12	428	12
Veldkamp <i>et al</i> ^[92]	627	10	621	10
Guillou <i>et al</i> ^[93]	526	12	268	13.5
Kang <i>et al</i> ^[94]	170	17	170	18
Braga <i>et al</i> ^[95]	134	14.5	134	15.3
Hewett <i>et al</i> ^[96]	294	13	298	13
Liang <i>et al</i> ^[97]	135	15.6	134	16
Leung <i>et al</i> ^[98]	203	11.1	200	12.1
Benhaim <i>et al</i> ^[99]	235	26.8	296	25.9

Only prospective or prospective randomized trials in over 250 patients. COST: Clinical Outcomes of Surgical Therapy Study Group; LNs: Lymph nodes.

ence between surgeon with greater and lesser experience compared to harvested LNs.

Indeed other authors consider this correlation inconsistent^[8,19,22,53,78,84-86] as it does not record statistical differences related to surgeon expertise or between colorectal surgeons and general surgeons, thus giving other authors^[9,87,88] the opportunity to dwell, instead, on the importance of an educational strategy that allows for a more accurate surgical technique. From this perspective, we must keep in mind that even though American studies^[36,46,69] have reported that a hospital's volume of surgery could affect lymph nodal sampling, Porter *et al*^[37] and Dejardin *et al*^[89] have recently reported that the simple implementation of guidelines within a center in addition to recommendations or the application of audit strategies may eliminate any differences between hospitals. This leads us to believe that a correct approach to the problem can bridge the "gap" between "current and best available evidence." The above authors' implication seems to reveal that a diligent surgical technique, which above all else ensures an adequate and "potentially measurable" sample of mesocolon^[21,41,87,88], can simply guarantee a sufficient number of LNs to be sampled. Whether the greater length of the intestine removed can determine more lymph nodal sampling is, in fact, a matter of controversy. While some authors lean toward this hypothesis^[19,21,78], others refute it completely^[90].

Although, as of present, literature has not offered conclusive data as to whether emergency surgeries are responsible for limited resections and hence smaller num-

bers of collected LNs^[19,40,56,86], more reliable data is available with regards to the influence of laparoscopic surgery on lymph nodal sampling, whose efficacy has been questioned. Actually, in addition to the COST^[91], COLOR^[92] and CLASICC^[93], other prospective randomized trials have opted for an overlap of the two techniques (Table 4). More significantly, a recent meta-analysis^[100] of 24 randomized trials has shown no significant differences between the two approaches concerning the number of LNs examined. On the contrary, Lujan *et al*^[101] has reported advantages in favor of laparoscopic surgery with regards to the number of LNs sampled in patients suffering from rectal cancer (13.63 vs 11.57, $P = 0.026$); similarly El-Gazzaz *et al*^[102] have reported, a greater number of metastatic LNs removed (2.2 ± 3.8 vs 1.6 ± 4 , $P = 0.03$), despite not being able to pin-point the exact reasons.

Pathologists: A review of the literature, even if there are still conflicting view points^[22,41,84], soon reveals that the diligence of a "pathology staff" (pathologists, pathology assistants, pathology residents, pathology technicians) could affect the number of LNs sampled^[10,11,21,35,50,53,60,61,79,86] and that the simple lack of time, more than the lack of educational training, especially seems to interfere with this data^[6,8,27,60,77]. This is indeed confirmed by the fact that, paradoxically, first-year "pathology residents"^[8] or "pathologists' assistants" who have "more time with fewer distractions"^[77] carry out better lymph nodal samplings than "pathologists", especially for cancer of the rectum.

Moreover, from the multivariate analysis of Leung *et al*^[98] we can deduce that pathologists and surgeons independently affect the lymph nodal sampling ($P < 0.05$ and $P = 0.01$ respectively) and that pairing surgeon/pathologist does not serve to compensate for the differences. Valsecchi *et al*^[21] also, in his analysis, support Leung's data^[98], but report for "surgeon's experience" a major risk factor ("OR = 2.33; 95%CI: 1.4-3.9, $P = 0.001$ " vs "OR = 1.9; 95%CI: 1.1-3.2, $P = 0.01$ " respectively) in contrast, Evans *et al*^[86] find no significant differences among surgeons but does so only among pathologists.

The possibility of having more time may also be useful for the implementation of procedures which have been widely recommended^[7,27,30,40]. Such procedures include the fat clearance technique or the intra-arterial injection of blue methylene, among others, which seem to improve performance. However, in addition to being costly^[11,23,27,60], these procedures are difficult to carry out

in centers with a high case volume^[3,23]. Therefore, while the NCCN^[39] recommends that if a pathologist samples < 12 LNs, a greater amount of tissue must be examined, the American College of Pathologists^[103] adds that in these cases the use of additional techniques is necessary even though there is still no consensus on the precise technique to be recommended.

In light of these considerations, especially for pathologists, it seems that, particularly in today's society, the "ceiling effect" must be reached (which is 12 or greater) in order to optimize time, costs and human resources.

Unmodifiable factors

Patient-related: The patient-related variables are among those for which there is less debate and difference of opinion. In the literature, in fact, it is agreed that advanced age could negatively affect lymph nodal sampling^[10,40,41,44,48, 50,53,60,80,104-108], decreasing by 9% for every 10 years of age^[107]. Among the hypotheses put forth, we must remember that surgery performed on a patient of advanced age cannot be extensive because of the presence of comorbidities^[3,10,40], in addition to the physiological involution of LNs^[10,40,56] and the weaker response of the immune system^[41].

Similarly, most authors^[19,22,36,85,90,107], with regards to gender, do not report a different LN retrieval while only some^[60,79,109] mention greater sampling in females.

Not all authors, on the other hand, are in agreement on the role that obesity may have during lymphadenectomy; some authors^[5,110], in fact, have shown either a higher LN retrieval in non-obese patients or a lower one in patients with high body mass index (BMI), probably due to the more difficult surgical dissection^[9,40,51,84]. Kuo *et al.*^[5], which refer in his experience as the BMI is associated with LNs harvest, highlights that the larger LN retrieval in non-obese patients is due to a bigger number of right colon cancers. However, the relationship between BMI and LN sampling still remains an open question. In fact many authors do not report such a correlation^[9,22,61,84].

Disease-related: Also with regards to the unchangeable disease-related variables, the literature is mostly consistent. All authors, in fact, agree that it is more difficult to achieve the target of 12 LNs when the tumor is located in the rectum, possibly due to the smaller size of the LNs, in spite of the higher percentage of malignant nodes retrieved^[3,53]. With regards to the colon, the number of LNs sampled is definitely higher in the right colon^[3,5,6,10,18,21,22,25,36,41,44,52,60,61,78,80,84,107,108] either because of the greater length of the mesentery root^[5,90] or due to a different embryological development that would ensure a greater number of LNs^[78].

Tumor characteristics have often been thought to have an effect on lymph nodal sampling; the greater the size and the more advanced the tumor staging (T and grading), the greater the number of LNs retrieved^[9,10,21,22,25,31,78,86,107], this probably due either to a greater immune response^[78] or to more aggressive surgery^[9,10].

When we consider, instead, the non-advanced tumors interesting is that recently report by Benhaim *et al.*^[99], the first in the literature, that determine the total number of LNs examined after colectomy for an endoscopically removed malignant polyp. In these patients the mean number of LNs examined was significantly lower compared to both patients operated for colon cancer at any stage (11.63 *vs* 26.23, $P = 0.0006$) and patients operated for colon cancer at pT₁ stage (11.85 *vs* 19.21, $P = 0.018$). Considering the fact that none of the patients who underwent a colectomy after endoscopic polypectomy showed a relapse, the authors suggest that the rule of 12 LNs can not be applied to malignant polyps as more than 12 LNs were examined in only 41% of patients who underwent a colectomy for such lesions.

It is also generally agreed^[3,56,80,86,107,111] that pre-operative radiotherapy is responsible for either a minor, absent, or at best widely variable lymph nodal sampling, irrespective of the characteristics of the patients or treatment^[17]. Evans *et al.*^[86], Deodhar *et al.*^[3], Tekkis *et al.*^[56] therefore refer to an average lymph nodal sampling of 7, 9.54 e 9.8 LNs respectively, while Doll *et al.*^[111], Govindarajan *et al.*^[112] and Rullier *et al.*^[113] report a statistically significant difference between patients treated with neoadjuvant radiochemotherapy or surgery alone (respectively 12.9 *vs* 21.4, $P > 0.0001$, 10.8 *vs* 15.5, $P > 0.001$, 13 *vs* 17, $P > 0.001$).

This appears to be due to inflammatory post-radiotherapy processes which cause stromal fibrosis of the LNs and of their subsequent reduction in size^[6,17,67]. Rullier *et al.*^[113] report that for every Gy of radiation, the sampled LNs number will be less than 0.21% and Norwood *et al.*^[19] show that this reduction is evident especially when pre-operative radiotherapy is used in combination with chemotherapy.

It is perhaps interesting to note that, in this case, the reduction in the number of sampled LNs, although oncologically favorable does not affect the survival rate but rather must be viewed as a positive response to neoadjuvant treatment^[6,111-113]. This has led some authors^[17] to conclude that the limit of 12 LNs is unrealistic for the stage of rectal cancer of patients who are treated with neoadjuvant therapy.

CAN THE "LYMPH NODAL RATIO" BE USEFUL IN THE EVENT OF INADEQUATE SAMPLING?

The seventh edition of the AJCC classification^[2], as mentioned previously, subdivides patients treated for colorectal cancer into prognostic categories according to the number of metastatic LNs. The accuracy of the staging is, however, influenced by the number of retrieved LNs that must be ≥ 12 . The lymph nodal ratio (LNR)^[49], which is the relationship between positive nodes divided by the total number of retrieved nodes, is in our opinion, justified mainly because it means not having to reach the so called "magic number." The LNR prognostic validity could in

fact be effective also in cases of reduced lymph nodal sampling^[12,16,45,114]. However, not all authors who have written on the subject agree^[6,43,49]. The LNR, independent of the number of LNs sampled, is also justified since, taken with the AJCC classification, it would allow us to subdivide, according to the risk involved, stage III patients reducing the excessive prognostic heterogeneity^[12,16,45].

In light of this, reviewing and taking into consideration the work of Bamboat *et al.*^[8], Qiu *et al.*^[12], Song *et al.*^[13], and Greenberg *et al.*^[114] in 2011, the LNR seems to be an independent prognostic factor in colorectal cancer, superior to the classification based only on N stage (number of positive nodes). In fact, based on the LNR analysis, Greenberg *et al.*^[114] himself state that the survival rate of stage III patients with favorable LNR is similar to that of stage II patients.

Conversely, Noura *et al.*^[42] only one year before published an interesting and somewhat more cautious editorial. In fact, the author reported that even though the LNR seemed to be a more reliable prognostic factor, its validity, in actuality, could not be completely agreed upon. In fact, clinical records were very different, randomized and multi-centric studies were lacking, and, most importantly, a uniformly valid cut-off was missing.

One thing is certain, given the importance of both the lymph nodal sampling and of the evidence of the lymph nodal metastasis, it is unthinkable that a pathologist could stop after “having found” the first neoplastic LN^[78]. However, it is not exactly clear what the “ceiling effect” is even in this case.

CONCLUSION

Despite the fact that numerous authors have expressed their opinions on the number of LNs sampled, it can be gathered that the number is between 6 and 40^[42]. Therefore, only in light of this wide range, should we all refer to the minimum number of LNs (now the obsessive “12”) which can allow us to avoid the so-called “Will Roger’s phenomenon”^[115] responsible for understaging.

Even if the surgeon and pathologist, as variables in the equation, could improve simply by standardizing surgical technique and by increasing the amount of time dedicated to this procedure, the other, more important variables^[22,31,114], namely patient and cancer-related, are not as easily modifiable. It is with these latter two variables in mind that we still pose the question whether it is possible, as we hope, to establish a universally valid cut-off node for all patients or whether it should instead be varied according to individual cases^[6,78].

Today, a valid perspective is still necessary for the identification of the sentinel LNs (at least 3)^[116]. This approach is based on the idea that the lymphatic flow originating from the tumor occurs “step by step”^[35,117] and the purpose of this technique in colorectal cancer would be not so much to modify the size of the resection, as has happened with other diseases, but for its “potential” effects on improving the staging^[29,31,40,41] since it would al-

low for more involved and expensive techniques on only a few LNs^[29,30,32,34] which would reveal micrometastases or isolated tumor cells.

The identification of the sentinel LNs, actually still remains a controversy among those authors who consider the mesenteric lymph drainage, especially in the rectum, too complicated^[32,40], and the majority of authors who, on the other hand, maintain that an aberrant lymphatic drainage occurs only in a small percentage of cases^[27,29,33,34].

As certainly interesting, the biological aspects of the tumor still remain the subject of speculation. Some authors suggest that reduced survival is not necessarily due to an inappropriate dissection performed by the surgeon and the pathologist, but may be linked to a cancer that is quite virulent and is hence responsible for a low immune response from the patient^[35,40,57,117]. Still, some other authors^[11,40,41,46,47,118,119] maintain that an elevated sampling could be determined by a vigorous immune response; this, in turn, is determined by the molecular instability of the tumor, which manifests itself as a high rate of “neo-antigens” and therefore causes a more limited neoplastic progression. Not coincidentally, these malignancies are located in the right colon^[41,44,118], where, as mentioned, more LNs are found.

As has already been pointed out, the obsession with the number 12 has its origins in studies which lack clear statistical evidence. Just as Curti *et al.*^[1] asserted that, as of 1998, not even a single prospective study had been published, authors still today are calling for prospective controlled studies that are, without question, difficult to predict both for a number of ethical reasons and for the sheer volume of clinical records. Hence, obtaining reliable data that would allow us to go beyond this obsession with the number 12 will not be easy.

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