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ARTICLE

Nodal Staging of Colorectal Carcinomas from Quantitative and Qualitative Aspects. Can Lymphatic Mapping Help Staging?

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Retrospective data analysis was performed to determine the minimum number of lymph nodes required for the staging of colorectal carcinomas, and a prospective feasibility study was carried out to identify sentinel nodes in order to clarify whether these may predict the nodal status. From among 240 colorectal carcinoma specimens investigated between 1996 and 1998, 224 tumors were analyzed for their nodal status. Lymphatic mapping with vital patent blue dye injection into the peritumoral subserosal layer was performed in 25 patients. Blue nodes were identified by the pathologist in the unfixed specimen immediately after the resection of the bowel and were assessed separately. Of the 123 node-positive carcinomas, 40 had more than 3 nodes involved. The nodal positivity increased substantially when more than 6 nodes were assessed. The cumulative percentage analysis demonstrated that ideally 16 and 13 nodes should be obtained for the identification of any nodal involvement or the involvement of more than 3 nodes, respectively. Lymphatic mapping was successful in 24 patients (96%). Blue nodes were predictive of the nodal status in 19 cases (79%), and were the only sites of metastasis in 2 patients (15% of the node-positive cases). Lymphatic mapping with the vital blue dye technique does not seem to facilitate the staging of colorectal cancers, at least in our patient population with relatively large and deeply infiltrating tumors, and unless the technique is improved or other selective features of lymph nodes are found, all lymph nodes should be assessed. A minimum of 6 nodes, and an optimum of 16 nodes or more, are suggested from these series. (Pathology Oncology Research Vol 5, No 4, 291–296, 1999)

Keywords: colorectal carcinoma, staging, sentinel lymph node, lymphatic mapping

Introduction

Metastasis to regional lymph nodes is an important prognostic factor in colorectal cancers (CRCs). It is an important feature of all major staging systems.[1,2,10,12] Patients with nodal involvement have a poorer prognosis and require adjuvant systemic chemotherapy. One of the most important factors in making the decision concerning adjuvant treatment is the presence or absence of lymph node metastases. However, the number of lymph nodes required for an adequate staging is still a matter of debate. There have been different suggestions in this respect, some investigators recommending the assessment of a minimum of 6 nodes, whereas others suggest as many as 17 nodes.[6,15] There is a strong suspicion that not only the number of lymph nodes investigated, but also some of their qualitative features may influence the likelihood of detecting metastatic disease in them. We have analyzed our data relating to CRC resection specimens from the last 3 years to test a mathematical model for the minimum number of lymph nodes required for staging, and also tested the identification of sentinel nodes (SLNs) in the pericolic fat as a possible means of selecting between lymph nodes and limiting the number of nodes examined by a consideration of their qualitative features, i.e. their proximity to the tumor on the basis of the physiological lymph draining paths.

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Abbreviations: AJCC: American Joint Committee on Cancer; CRC: Colorectal cancer; SLN: Sentinel lymph node; UICC: Union Internationale Contre le Cancer

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Materials and Methods

All specimens from resected primary CRCs assessed at the Department of Pathology of Bács-Kiskun County Hospital between January 1996 and December 1998 were retrieved from our archives. The clinicopathological features of the tumors were analyzed with emphasis on the nodal status.

All these tumors were staged in 3 systems: the original scheme described by Dukes,[10] the modified one described by Astler and Coller,[2] and the TNM system of the UICC and AJCC.[1] Nodal involvement was expressed in terms of the number of nodes examined and the number harboring metastases. The AJCC guidelines were followed in identifying metastatic nodes.[1] All lymph nodes recovered from the resection specimens were subjected to histopathology; this involved the investigation of hematoxylin and eosin-stained slides from the central cross-section of the nodes. Metastatic involvement was then assigned to categorical groups of N0 (node-negative), N1 (1 to 3 metastatic nodes) or N2 (more than 3 metastatic nodes), irrespective of the localization of the lymph nodes.

The data were next analyzed in a mathematical model that has already been used in the context of CRCs[15] and breast cancers.[8] We attempted to identify the minimum number of lymph nodes to be examined for the adequate staging of CRCs on the basis of the distribution of the examined nodes in relation to metastatic disease.

Besides this purely mathematical and quantitative model, we also set out to assess the nodal status from a more qualitative approach, by attempting to identify the SLNs draining the tumors. For this, 2 ml of patent blue dye (Patentblau V2.5%, Byk Gulden, Konstanz, Germany) was injected subperitoneally in the close vicinity of the tumors, after the bowel segment had been isolated and mobilized. The resection was then completed and the specimens were sent to the histopathology lab, where they were cut up in the fresh state. As for the retrospective study, no fat clearing technique was used, but the mesocolic/perirectal fat was separated from the bowel wall and thoroughly palpated. All blue nodes were separated from the remaining unstained nodes, and their metastatic contents were reported separately. Although the literature is controversial in this regard, there are publications suggesting that the nodal involvement of CRCs does not seem to require an extensive search for micrometastases.[16,25] As our aim was not the microstaging of CRCs, but the evaluation of the distribution of metastases in the blue nodes and the unstained nodes, only 2-3 central sections stained with hematoxylin and eosin were used for the investigation of all nodes recovered. As this was a feasibility study, in order to assess the possibility of a more adequate staging model incorporating not only the number of assessed nodes, but also one of their qualitative features, i.e. their being a first echelon node, patients were not selected for the procedure. The only selection criteria considered were the lack of a skin reaction to intradermal testing with the dye, and informed consent being given.

Results

A total number of 232 patients (126 males and 106 females) were selected from the archives. Their median age was 68 years (range: 37-90; mean 66.3). The stage and depth of invasion of their disease is demonstrated in *Table 1*. There were 8 synchronous double tumors in the series; 7 of these pairs were assessed in conjunction because of their close localization. Only the largest of these duplicate tumors with the deepest infiltration were considered further.

The number of lymph nodes recovered from the resection specimens increased during the study period (*Table 2*), probably because of increased awareness of the adequacy of nodal staging. The distribution of specimens with a given number of lymph nodes examined is displayed in *Figure 1*.

From the 224 tumors analyzed, 101 were node-negative and 123 had metastases in the regional lymph nodes; 40 of the latter had more than 3 nodes involved. *Figure 2* shows

Table 1. **Distribution of colorectal cancers by stage and pT and pN categories**

Dukes		*Astler-Coller*		*pTpN*	
A	32	A	4	Tis	4
B	85	B1	36	T1Nx	5
C	123	B2	77	T1N0	6
		C1	5	T1N1	1
		C2	118	T2Nx	1
				T2N0	25
				T2N1	1
				T2N2	1
				T3N0	76
				T3N1	71
				T3N2	37
				T4N0	1
				T4N1	5
				T4N2	2
Total	240		240		240

Table 2. **Lymph node recovery rates during the study period**

		Number of lymph nodes examined	
Year	*Number of tumors*	*Range*	*Mean*
1996	61	0–16	6.9
1997	76	0–31	9.7
1998	95	0–34	9.6
Total	232	0–34	8.9

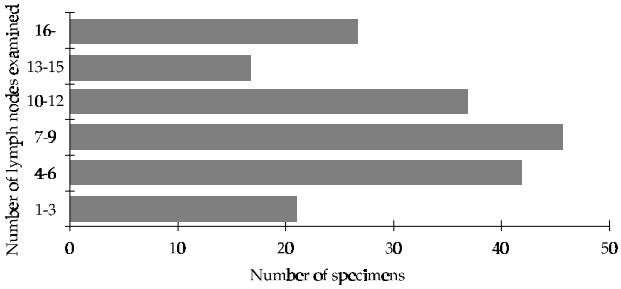

Figure 1. Distribution of lymph nodes recovered during the period of the retrospective study

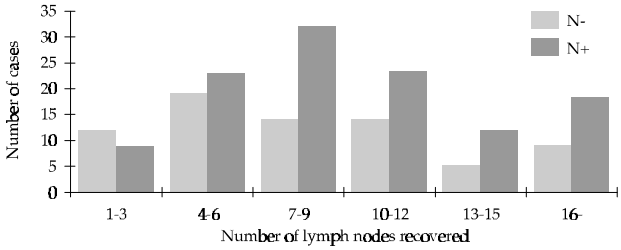

Figure 2. Distribution of node-negative (N-) and node-positive (N+) cancers in relation to the number of nodes examined

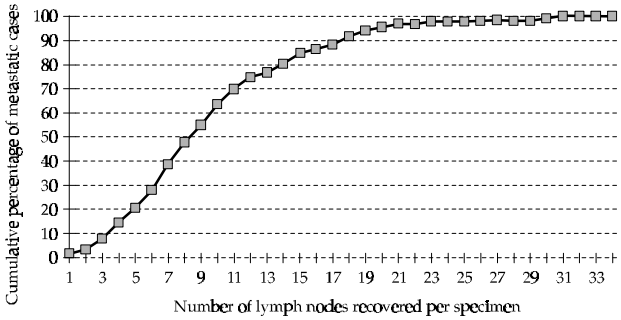

Figure 3. Cumulative percentage of node-positive colorectal cancers in relation to the number of lymph nodes examined

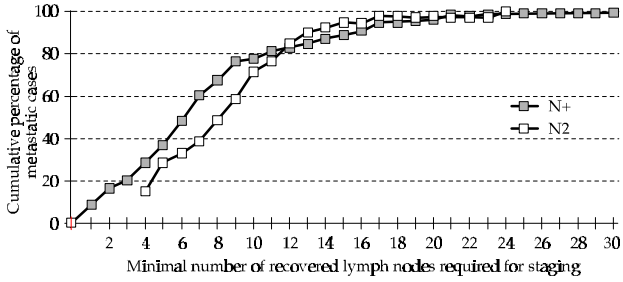

Figure 4. Cumulative percentage of node-positive colorectal cancers in relation to the minimal number of lymph nodes required for staging. (N+: any nodal involvement; N2: more than 3 metastatic nodes)

the relationship between the number of recovered lymph nodes and the qualitative nodal status (negative or positive for metastases). It suggests that, if the number of examined nodes is 0–6, the probability of a false nodal staging is considerable, as the number of node-positive cases is less than that of node-negative ones. Examining more than 6 nodes results in a better staging accuracy, as an increase in the detection of regional metastatic disease is seen with 7 or more lymph nodes harvested.

The cumulative percentage of nodal involvement in relation to the number of nodes examined is demonstrated in *Figure 3*. This curve suggests that at least 90% of the tumors demonstrating metastases to regional lymph nodes could be identified by examining 18 nodes. While *Figure 3* considers data for the demonstration of any nodal involvement in relation to the number of recovered lymph nodes, *Figure 4* takes into account the number of metastatic nodes. It is assumed that at least 1 metastatic node is identified if the number of nodes assessed = the number of lymph nodes recovered - the number of metastatic nodes + 1. To categorize all the true N2 group as such, the number of lymph nodes recovered - the number of metastatic nodes + 4 nodes must be examined. From *Figure 4*, the investigation of 16 nodes is suggested for the identification of at least 90% of tumors with any nodal involvement (Dukes C, Astler-Coller C2) and 13 would be required to identify at least 90% of the N2 subgroup.

We investigated 25 tumors of unselected patients with patent blue lymphatic mapping. The tumors were staged as follows: 2 Dukes A, 10 Dukes B and 13 Dukes C (alternatively: 2, 10 and 13 Astler-Coller B1, B2 and C2, respectively, or 2, 10, 7 and 6 pT2pN0, pT3pN0, pT3pN1 and pT3pN2, respectively).

The median number of lymph nodes recovered was 15 (range: 2–34, mean: 15.5). From these, a median of 4 (range: 0–12, mean: 4) were stained blue, and labeled as probable SLNs. The number of blue-stained particles removed as lymph nodes was somewhat higher, but some of these contained no lymphatic tissue at all, and comprised merely fat or vessels.

The distribution of metastases in presumed SLNs and non-blue nodes is shown in *Table 3*. By analyzing data in *Table 3*, the sensitivity (62%), negative predictive value (69%), overall predictive value (79%) and false negative rate (38%) of the blue nodes in relation to the overall nodal status can be calculated. The specificity and positive predictive value are by definition 100% in this setting as node negativity cannot occur in case of a positive blue node.

Discussion

There have been several suggestions as to the number of lymph nodes to be investigated histologicaly for a better staging of CRCs. These models have suggested different

numbers, ranging from 6 to 17.[11,15,17,22,23,28] The AJCC Staging manual proposes 12 as the optimal minimum.[1] Clearing techniques may increase the number of lymph nodes harvested,[16,28] but their costs and extra workload makes them unsuitable as routine procedures. Our analysis (*Figure 2*) has demonstrated that the investigation of 0–6 nodes leads to a smaller proportion of node-positive cases than the investigation of more than 6 nodes. A study based on survival analysis also suggests that patients with Dukes B CRCs with 6 or less nodes examined have a poorer survival, probably because of the false node-negative staging.[6] Our results are in keeping with this conclusion.

On the other hand, we also analyzed our data in a descriptive way, by considering the maximal mathematical probability of identifying any nodal involvement to be the minimal oncological or staging requirement. It is obvious that the identification of 1 metastatic node from *n* recovered nodes can be achieved by investigating the only metastatic node in the optimal setting, or by investigating the number of recovered nodes - the number of metastatic nodes +1 node in a less fortunate case. In this way, we could identify a limit of 16 nodes or 13 nodes for the identification of at least 90% of patients with 1 or with more than 3 metastatic nodes, respectively.

Table 3. **Basic data on tumors studied by lymphatic mapping and their nodal status**

No.	*Sex*	*Size*	*pT*	*LI*	*SLNs*	*Non-SLNs*
1	f	2	pT3		3 (0)	9 (0)
2	f	4.5	pT3		3 (0)	3 (1)
3	f	4.7	pT3		5 (2)	9 (0)
4	m	ni	pT3		3 (0)	0 (0)
5	f	4	pT3		7 (2)	16 (9)
6	f	4	pT3		6 (0)	5 (0)
7	m	10	pT3		6 (0)	11 (4)
8	f	4.5	pT3	+	4 (4)	13 (3)
9	f	9	pT3		5 (4)	10 (0)
10	f	7	pT3		2 (0)	32 (0)
11	m	7	pT3		0 (0)	4 (0)
12	m	3.5	pT3		4 (0)	5 (0)
13	f	7	pT3		1 (0)	22 (0)
14	f	5.5	pT3	+	2 (0)	20 (1)
15	m	3	pT3	+	5 (1)	15 (11)
16	m	4.2	pT3		9 (4)	20 (2)
17	m	11	pT3		1 (1)	21 (1)
18	f	6.5	pT3		7 (0)	9 (1)
19	f	3.2	pT2	+	12 (0)	0 (0)
20	m	5	pT3		5 (0)	7 (0)
21	f	9	pT3	+	7 (0)	11 (1)
22	m	6.5	pT3		3 (1)	18 (2)
23	m	2.8	pT3		4 (0)	16 (0)
24	m	2.1	pT2		1 (0)	1 (0)
25	f	12	pT3		5 (0)	12 (0)

(No.: patient number in consecutive sequence; f: female, m: male; size: largest tumor dimension in cm; pT: pT category of the tumor [1]; LI: lymphatic invasion; +: present; SLNs: sentinel lymph nodes; number of metastatic nodes in parentheses.)

As pointed out earlier,[9] these quantitative approaches have several shortcomings, e.g. always involving a substantial number of tumors being staged on the basis of a suboptimal number of lymph nodes, or the shift to the right in the suggested optimal limit on increase of the number of examined nodes. This is why we investigated the possibility of a more qualitative approach, by trying to identify the SLNs draining the tumors in question.

The SLN concept was first formulated in penile carcinoma,[5] and then extensively analyzed in two other settings after the pioneering work of Morton, Krag, Giuliano and their colleagues[14,20,24]: malignant melanomas of the skin and early breast cancer. Other tumors, such as thyroid carcinomas,[19] and oral and gynecological cancers have also been investigated [21](The sentinel node biopsy. A new strategy for lymph node dissection in breast cancer, melanoma, gynecological, lung and head and neck carcinomas. - Milano, September 28, 1998). Although there are serious limitations in identifying the SLNs in some localizations, such as the lungs, it seems that the concept can be uniformly applied to most solid tumors.[3] It is stated that mapping the lymphatic paths draining the tumors by vital blue dyes or radiolabeled colloids permits identification of the first echelon nodes (SLNs). These are the most likely to harbor metastases, as demonstrated by multiple series, and their negativity makes it very likely that the remaining regional lymph nodes are also free of tumor. The identification of SLNs may allow them to be subjected to a more extensive histopathological work-up. Thus, SLNs can afford a better staging and may result in omission of the investigation (and/or removal) of the remaining lymph nodes if the SLNs are negative.[13] However, this last statement must be confirmed by ongoing prospective clinical trials with large numbers of patients and a substantial follow-up.

Many series have documented a learning curve in the identification of SLNs in connection with other types of tumors. Our series do not reveal such a curve, and this can be explained by our methods. The identification of all nodes was performed by the pathologists with the same care. From the recovered lymph nodes, those stained blue were identified as probable SLNs. We did not have to learn how to follow blue lymphatics during dissection. However, a learning curve can be expected if the surgeon looks for the blue nodes intraoperatively.[18]

Our series indicates a high rate of false-negativity (defined as negative blue nodes and metastatic non-blue nodes), and points to the limitations of identifying SLNs in CRCs. Lymphatic invasion was seen in 5 tumors and extensive lymphatic invasion is reported to be a major lim-

iting factor in the context of breast carcinomas.[29] Extensive nodal involvement, including total destruction of the nodes by metastases, can also compromise the identification of true SLNs, similarly to the phenomenon observed with breast cancers.[4] Moreover, the size of the tumors may probably also play a role in the correct identification of SLNs, a fact that has likewise been described in the context of breast carcinomas. Larger tumors or biopsy cavities have a higher chance of being associated with false-negative SLNs.[4,7,26,27] The timing of the vital blue dye injection prior to resection may also be a crucial problem. A 15–25-minute latency (depending on the intraoperative situation) may allow overflowing of the dye, but would probably not result in complete decoloration of the first stained node. Direct tumoral spread through the bowel wall may compress and alter the original lymphatic flow, deviating the vital blue dye from the original SLNs. If this were to prove the case, this would be a major limitation of lymphatic mapping in most of the pT3 and pT4 tumors, which have the highest frequency of being node-positive. On the other hand, there is growing evidence that patients with pT3 tumors benefit from adjuvant chemotherapy irrespective of their nodal status. This is why lymphatic mapping should be further studied in pT1 and pT2 tumors, of which only 1 and 5 were positive in our retrospective analysis, respectively. Microstaging of SLNs in such tumors through serial sectioning and immunohistochemistry may reveal a subset of patients who may also benefit from adjuvant chemotherapy.

CRCs have not been extensively studied for the applicability of the SLN theory, but we are aware of a paper by Saha and colleagues from Michigan State University reporting on 56 patients with CRCs (17th International Cancer Congress, August 23–28, 1998, Rio de Janeiro). Lymphatic mapping was performed with isosulphan blue (Lymphazurin 1%) administered into the subserosal layer around the tumor, and the first 1–3 blue nodes identified were denoted as SLNs. Identification was successful in 55/56 cases. One, 2 and 3 SLNs were found in 29, 22 and 4 cases, respectively. From the 21 patients with nodal involvement, only 2 had false-negative sentinel nodes (9.5%). However, the size of the tumors was not specified in that series, and this may be a major difference. Although the tumor size seems to lack prognostic significance in CRCs, if the depth of invasion is also considered,[30] it probably influences the results of lymphatic mapping. Minor technical differences may also have an impact on the results.

A recent study involving 50 CRCs mapped with patent blue found a low intraoperative identification rate (70%), a high false-negativity rate (60%), and a low positive predictive value (55%) for the blue nodes. It was concluded that SLN identification in CRC patients is unreliable.[18] This is in keeping with our results.

In conclusion, we have demonstrated that the examination of 6 or less nodes may lead to the understaging of CRCs, and especially of pT3pN0 and pT4pN0 (Dukes B) CRCs. Our series indicates the need to assess at least 16 lymph nodes for the identification of most tumors with nodal involvement, and at least 13 nodes for the identification of extensive nodal involvement (4 or more metastatic lymph nodes). However, such numeral limits based on the mathematical analysis of retrieved nodes reflect only the reliability of staging, and all removed lymph nodes must be examined, unless a selection can be made on the basis of qualitative features. The identification of SLNs draining the tumors may be such an alternative approach. However, our preliminary results highlight many of the limitations of lymphatic mapping, including extensive lymphatic and nodal involvement and relatively large tumor size. Due to the unfavorable sensitivity, false negative rate and negative predictive value, blue nodes identified in the study population by our technique cannot be termed as true SLNs. Until other techniques of SLN tracking (e.g. gamma-probe guidance) are tested, or the limitations of our technique are overcome, or other qualitative features (e.g. size and/or localization of the nodes) are found to allow a selection, we must retain the standard procedure of recovering and microscopically examining all removed lymph nodes for the staging of CRCs. SLN identification in pT1 and pT2 tumors deserves further studies.

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