Cirujano General

Volumen *Volume* 26 Número *Number* 1 Enero-Marzo *January-March* 2004

Artículo:

Lymphatic mapping and sentinel node biopsy in gastrointestinal neoplasms

REVIEW ARTICLE

Lymphatic mapping and sentinel node biopsy in gastrointestinal neoplasms

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Abstract

Objective. **To discuss whether available information supports lymphatic mapping and sentinel node histology as a useful tool to grade gastrointestinal (GI) malignancies.**

Data collection. **Selective review of the literature. (Thirty-five references)**

Data sellection. **The most relevant paper dealing with lymphatic mapping and sentinel node biopsy were selected.**

Setting: **Third healt care level hospital**

Results. **The use of lymphatic mapping and sentinel node biopsy has been validated in melanoma and breast cancer. Recently, this staging scheme has been implemented for other solid tumors including neoplasms of the gastrointestinal (GI) tract. Lymph node mapping has two salutary advantages: reduction of morbidity associated with the use of conventional staging lymphadenectomy, while staging accuracy remains unaffected. Early experience with lymphatic mapping for neoplasms of the GI tract, following the introduction of the sentinel lymph node concept, indicates that this approach is feasible and, like in breast cancer and melanoma, can also identify micrometastatic malignancies of the GI tract. Reported series have shown identification rates ranging between 85% and 97%. These numbers are higher than the preliminary reports for melanoma and breast cancer. However, the biological implication of micrometastases remains debatable and further studies/evaluation about the role of lymph node mapping based on sentinel biopsy for GI neoplasms is required.**

Conclusion. **Current information indicates that lymphatic mapping and sentinel node biopsy have the potential to identify important nodes in the region of a tumor. Furthermore, the focused analysis of harvested sentinel nodes can improve tumor staging.**

Resumen

Objetivo: **Discutir si la información disponible apoya el mapeo linfático y la histología del nódulo centinela como una herramienta útil para estadificar las neoplasias malignas gastrointestinales (GI).**

Obtención de datos: **Revisión selectiva de la literatura (35 referencias).**

Selección de datos: **Se escogieron las publicaciones más relevantes sobre mapeo linfático y biopsia de nódulo centinela.**

Sede: **Hospital de tercer nivel.**

Resultados: **El uso de mapeo linfático y biopsia del nódulo centinela ha sido convalidado en el melanoma y cáncer de mama. Recientemente, se ha implementado este esquema de estadificación para otros tumores sólidos, incluyendo neoplasias del tracto gastrointestinal. El mapeo del nódulo linfático tiene dos ventajas: reducción de la morbilidad asociada al uso de la estadificación convencional mediante linfadenectomía sin afectar la exactitud. La experiencia inicial con el mapeo linfático para las neoplasias del tracto GI, después de la introducción del concepto de nódulo linfático centinela, indica que este enfoque es posible y, tal como en el cáncer de mama y el melanoma, puede también identificar malignidades micrometastásicas del tracto GI. Las series publicadas han mostrado tasas de identificación entre 85 y 97%. Estas cifras son más elevadas que los informes preliminares para melanoma y cáncer de mama. Sin embargo, la implicación biológica de las micrometástasis se sigue debatiendo y se requieren más estudios y/o evaluaciones sobre el papel que desempeña el mapeo de nódulo linfático basado en biopsia del nódulo centinela para las neoplasias malignas del tracto GI.**

Conclusión: **La información actual indica que el mapeo linfático y la biopsia del nódulo centinela tienen el potencial para identificar nódulos importantes en la región del tumor. Además, el análisis centrado en los nódulos centinelas cosechados puede mejorar la estadificación del tumor.**

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Recibido para publicación: 10 de enero de 2003.
Aceptado para publicación: 16 de abril de 2003.

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Key words: Lymphatic mapping, sentinel lymph node, gastrointestinal cancer.
Cir Gen 2004;26: 23-28

Palabras clave: Mapeo linfático, nódulo linfático centinela, neoplasias gastrointestinales.
Cir Gen 2004;26: 23-28

Introduction

Lymphatic mapping, based on sentinel node biopsy, has been utilized in various types of malignancies as such as melanoma, breast, head, neck, and penile cancer. This procedure has been introduced in order to improve tumor staging, while morbidity associated with conventional lymphatic node dissections remains unaffected. More recently, the sentinel node concept has been applied to stage cancer of the gastrointestinal (GI) tract.

Cabanas originally introduced the concept of sentinel lymph node in 1977. He defined it as the first lymph node to receive metastases from the primary tumor.[1] He observed that, in carcinoma of the penis, lymph nodes in close proximity to the superficial epigastric vein were the first to be invaded by metastatic tumor cells, before involvement of other nodal groups, including the inguinal nodes. No further studies were performed, and the idea was abandoned for many years until the late 80's when Morton applied the procedure to stage malignant melanoma.[2]

From that point in time, the importance of lymphatic mapping, based on the conception of sentinel lymph node, has been accepted for malignant melanoma. Subsequently, Giuliano and associates introduced the procedure to breast cancer;[3] and more recently, Bilchik and coworkers have used it in a variety of solid neoplasms.[4] Lymph node status in GI cancer, like melanoma and breast cancer, is relevant for prognosis and treatment of these pathologies.[5-7] Following the major progress obtained with innovative surgical procedures along with adjuvant therapies; accurate information about disease stage, based on lymph node spread is essential for cancer management in these patients. Currently, complete regional lymph node dissection with histologic examination of the specimen, is the staging practice most widely employed for the management of GI neoplasms. The accuracy of this approach is unquestionable; however, extensive lymphadenectomy, which has to be performed on all patients, carries a significant morbidity, particularly in cases of extended D2 resections.[8]

Recent reports indicate that lymphatic mapping and the recognition of sentinel lymph nodes may provide accurate staging in gastrointestinal neoplasms.[4,6,9] Nonetheless, feasibility and reliability of this approach in the GI tract remain unclear and controversial. The aim of this review is to discuss whether available information supports lymphatic mapping and sentinel node histology as a useful tool to classify GI malignancies.

Lymphatic mapping and techniques of sentinel node identification

The purpose of intra-operative lymphatic mapping and sentinel node dissection is to provide a useful method for both tumor staging and recognition of patients who need extended regional lymphadenectomy, as part of the surgical management of the primary malignancy. There are several techniques for lymphatic mapping and sentinel lymph node sampling. The simplest and oldest one involves intra-operative mapping with vital blue dye, such as isosulfan blue or Patent blue-V.[2,10] Isosulfan blue is the 2,5-disulfonated isomer of Patent blue. Both dyes share comparable pharmacocynetic features. However, some surgeons rather favor the use of Patent blue-V as an alternative to isosulfan blue. One offered reason for this preference is that Patent blue-V dye is more concentrated.[2] The incidence of allergic reactions to both dyes has been reported to be very low.[2,10] The exact frequency of these adverse reactions is unknown but has been estimated to be between 0.6% and 2.5%.[11] However, allergic reaction can be severe and include facial and glottic edema with either respiratory distress, shock or anaphylaxis.[11,12]

Lymphatic mapping of GI malignancies involves injection of 0.5 to 2 ml of blue dye into the subserosa, around the tumor with a tuberculin syringe. For low rectal cancer, Keshtgar and co-workers recommend injecting the patent blue dye into the submucosa around the tumor through a proctoscope.[13] In as much as 5 minutes, after injecting the blue dye, an afferent lymphatic channel can be seen, as well as staining of the first lymph nodes (sentinel node). These nodes are dissected out and examined for deposits. With this technique, identifying sentinel nodes and lymphatic channels may not be an easy task, since rapid clearance of blue dye occurs. Thus, there is only a short time interval, during which selective identification of the sentinel node by the surgeon is possible. Not surprisingly, the rate of sentinel node recognition with blue dye varies widely, with reported success rates ranging from 60% to 96%.[2,3,14] The most important causes of failed recognition include injection of inadequate amounts of blue dye, inappropriate timing for starting the excision, atypical lymph drainage, and obstruction of lymph flow due to tumor invasion.[15,16]

Another technique of lymphatic mapping that has been employed is referred as "radiocolloid lymphoscintigraphy". Once more, it requires peritumoral injection of radioactive colloid. Currently, there are many radiocolloid preparations distributed worldwide; although the one most frequently utilized is technetium-99m Sn (tin) colloid.[13] Radiocolloid lymphoscintigraphy can be employed either preoperatively or during surgery. It can also be used in combination with vital blue dye injection. The preoperative approach is specially useful in cases where the primary tumor may have ambiguous drainage.[17,18] With this technique, it is possible to identify areas of increased radioactivity (hot spots) in nodes and lymphatic routes of unexpected regions. A "hot" lymph node is defined as any lymph node with an *in vivo* radioactivity count three

times greater than the background, or an *ex vivo* count 10 times greater than the background.[19] The presence of a positive lymphoscintigram before the operation is a strong predictor for a successful sentinel node biopsy.[20] The intra-operative technique is similar to the one used with isosulfan blue dye. Though, the surgeon uses a hand-held gamma counter to trace both lymphatic channels and sentinel nodes. This technique allows better identification of sentinel nodes with a lesser dissection. The endoscopic submucosal injection is the rout most commonly used for the administration of the radiocolloid. The injection procedure is almost the same as the mucosa/lesion-elevation technique used for endoscopic mucosal resections. After the injection of the radiocolloid, radioactivity is measured with the hand-held probe in counts per second. The first sentinel node and other "hot nodes" are harvested and all are included as sentinel nodes. The activity of these nodes is measured *ex vivo*, and ratios are then determined. The final step involves rechecking the background for radioactivity, and further dissection for location of sentinel nodes is completed at areas of radioactivity greater than 150% over the background count.[19]

The combined use of preoperative radiocolloid lymphoscintigraphy and intraoperative injection of blue dye can increase lymphatic mapping success.[14,19,20] With the combined technique, success rates between 84% and 96% have been reported for melanoma; contrary to a 70% average for lymphoscintigraphy alone. The higher success rates are clearly determined by both the visual (blue dye) and quantitative tests practiced by the surgeon. This ensures complete removal of every sentinel node.

Therefore, surgeon's experience is one of the most important factors for successful sentinel node recognition. Morton et al. established that surgeons were able to improve their technical skills in identifying sentinel nodes as they gained more experience.[2] This was further supported by Kollias et al. who demonstrated that more experienced surgeons achieve consistent higher successful rates (89% to 95%), while less experienced surgeons reach only a 66% successful rate.[20] The learning curve of sentinel node mapping in breast cancer indicates that one surgeon needs, on average, 23 cases to achieve a 90 ± 4.5% success rate, and as much as 53 cases are required to achieve a 95 ± 2.3% success rate.[12]

The sentinel node in esophageal cancer

The extent of lymphatic metastases is an important predictor for survival in esophageal cancer. Accordingly, careful evaluation of lymph node metastases is essential when deciding the therapeutic strategy for patients with esophageal cancer. Node metastases are diagnosed either for their size estimated by computerized tomography (CT), by endosonographic findings, or by node biopsy through minimal access surgery.[5,21] Although, CT scan has poor sensitivity, and endoscopic ultrasound is not well tolerated by the patient. On the contrary, node biopsy obtained by minimal access surgery has been shown to provide accurate pre-resection staging as well as good tolerability.[22] The use of sentinel node biopsy in esophageal cancer has only been reported recently. Kitagawa et al. reported results and diagnostic significance of sentinel node mapping in 85 cases of GI cancer. Esophageal cancer was detected in sixteen cases. While, sentinel nodes were detected in 88% of them, with sensitivity and accuracy rates of 88% and 92%, respectively. The occurrence of lymph node involvement with metastases was 27% for sentinel nodes and 2% in non-sentinel nodes.[17] These results are better than those obtained with CT scan, and similar to the results observed with endoscopic ultrasonography.

This has been the only published paper reporting the use of sentinel lymph node concept and lymphatic mapping technique for esophageal malignancies. Yet, it is too early to reach any conclusions about their clinical importance, as more research and reported experience are required. The procedure also offers an opportunity to improve our knowledge on the behavior of esophageal cancer.

The sentinel node in gastric cancer

Staging gastric cancer by means of sentinel lymph node sampling has produced considerable debate, and the issue is by no means resolved.[4,6,23-24] One important reason is related to the nature of lymphatic drainage of the stomach, which is far more complex than that of breast and skin. Thus, nodal metastases can occur haphazardly in gastric cancer, and sometimes second and third nodal levels are involved, leaving level one (nodes closest to primary tumor) nodes free of metastatic disease (skip metastases). The documented incidence of "skip" metastases would appear to limit the value of lymphatic mapping.[17,23,25]

Early reports by Catarci and coworkers provide indirect support for the sentinel node concept in gastric cancer.[26] They performed preoperative endoscopic vital staining with a suspension of activated carbon particles. The idea was to allow the surgeon to perform a more extensive lymphadenectomy, that is, to remove a higher number of lymph nodes during gastric resection for cancer. Subsequently, Kosaka and associates performed a retrospective revision whose main goal was to describe lymphatic spread routes in patients with solitary lymph node metastasis.[25] In this study of 735 patients with gastric cancer, only fifty-one patients (6.9%) had solitary lymph node metastasis, and seven (14%) out of 51 solitary lymph nodes had "skip" metastases. Lymph node groups located along the left gastric artery (station 7) and those along the common hepatic artery (station 8) were the places most commonly involved with "skip" metastases.[25,27]

Maruyama and coworkers also reported these stations as the most commonly affected nodal groups in gastric cancer.[23] Although, they injected dye in the gastric wall in order to outline regional lymphatic drainage anatomy, including the lymphatic vessels. They found that dye failed to stain all nodes encompassing lymphatic drainage. This was attributed to the occurrence of multiple lymphatic by-pass, which accounted for the documented "skip" lymph node deposits.[23] Kitagawa and colleagues also reported the presence of skip metastases in gastric cancer.[17] Sentinel nodes were found in the second and third compartments in 40% of the cases. Furthermore, diffi-

cult to detect occult micro-metastases may be the source of skip involvement.[23,25] Not surprisingly, the frequency of this problem is unknown. Identifying these micro-metastases requires methods of immunohistochemistry and other more specific and expensive molecular biology techniques, such as reverse transcriptase-polymerase chain reaction (RT-PCR).

Despite the high rates of skip metastases reported in GI malignancies, especially in gastric cancer, outcome and diagnostic significance of sentinel node mapping have shown a satisfactory detection rate **(Table I)**. Kitagawa and colleagues reported 100% accuracy and 100% sensitivity with 97% sentinel nodes being identified in thirty-six cases of gastric cancer.[17] Tsioulias and coworkers also reported acceptable detection rates. They established that histological grading of sentinel nodes accurately predicted both tumor stage and loco-regional lymph node involvement in 100% of patients with gastric cancer. False negative results were not observed with sentinel node biopsy.[6]

These studies, although few in number, demonstrate that lymphatic mapping and sentinel node biopsy in gastric cancer is feasible. Though, definite conclusions are not possible; and concern regarding micro-metastases leading to skip involvement still persists. If micro-metastases in lymph nodes are overlooked, which is possible with routine hematoxylin and eosin (HE) staining, gastric cancer understaging will result. The strength of sentinel node mapping relies on its ability to spot those lymph nodes carrying the greatest risk for nodal deposits.[28] Thus, careful study of harvested sentinel nodes enhances micro-metastases detection rates. This in turn allows accurate staging and improved outcomes with the use of adjuvant therapy.[6,28]

The sentinel node concept in colorectal cancer

The sentinel node concept and lymphatic mapping were introduced with encouraging results in colorectal cancer.[6,9,15,17,28] To date, the largest and single center experience reported in the literature is the prospective study by Saha and coworkers.[9] They successfully identified sentinel nodes in 99% of the patients with colorectal cancer. Furthermore, ninety-four percent of patients whose sentinel nodes were free of tumor deposits had all other non-sentinel nodes negative for metastases. Sensitivity, specificity and false negative rates for sentinel node mapping in this study were 91%, 100%, and 9%, respectively. Tsioulias and associates found similar results in a series of 50 patients with colorectal cancer.[6] Successful and false negative rates were 94% and 9%, respectively. In contrast, the clinical trial by Joosten and associates does not support sentinel node biopsy. They reported false negative results in 60% of the cases.[16] Nevertheless, the poor methodology of their study may have contributed to these false negative results.

The surgical approach for melanoma and breast cancer changed after the introduction of sentinel node biopsy.[2,3,29] In both cases, the decision on whether or not performing lymphadenectomy relies on the biopsy itself. Thus, the procedure has effectively replaced routine regional lymph node dissection for nodal staging.[29] Contrary to breast cancer and melanoma, lymphadenectomy, which is an essential part of the surgical procedure for colon cancer, has no associated morbidity.[29,30] Therefore, the importance of sentinel node biopsy in colorectal cancer is limited to improving disease stage rather than to determine the extent of resection.[6,9] However, it may be helpful to decide the need of adjuvant therapy. In this regard, there are many reports suggesting that colorectal cancer may be under-staged. The rational for this argument is that histopathological sampling and gross anatomy of lymph nodes in the mesentery may miss out critical nodes that may as well contain occult metastases. Up to 100 lymph nodes sections are cut 6 ìm-thick, and no more than 1 or 2 sections are selected for examination by light microscopy. Therefore, the possibility of missing out occult metastases is high.[29] This is the most common reason for histopathological under-staging in colorectal cancer.

Lymphatic mapping and focused analysis of sentinel nodes have been proposed as the preferred method to reduce neoplasm under-staging.[6,9] In the study by Tsioulias and associates, focused analysis of sentinel nodes upstaged 23% of gastrointestinal malignancies.[6] Routine HE staining confirmed nodal metastases only in a small number of specimens. Micrometastases were identified with additional analysis of multiple sections and the use of immunohistochemistry. The importance of focused analysis was further supported by Saha, and Bilchik,[9,31]

The sentinel node in minimal invasive surgery

The accepted surgical management of GI malignancies has been "en bloc" resection plus regional lymphadenectomy. The extent of lymphadenectomy varies widely, ranging from D_1 to D_3 resections. Curative resections

Table I
Diagnostic significance of sentinel node (SN) mapping in gastrointestinal malignancies.

Authors	False Negative (%)	Accuracy (%)	Sensitivity (%)	SN identified (%)
Kitagawa et al[16]	—	95	87.6	90
Tsioulias et al[6]	4	96	89	95
Joosten et al[15]	60	—	—	70
Bilchick et al[4]	14	—	—	78
Saha et al[8]	9	95	91	98.8

performed by laparoscopy are specially appropriate for early stages of disease, where lymph node metastases have been excluded by means of intraoperative sentinel node biopsy. Kitagawa, using a laparoscopic gamma-probe in patients with gastric cancer, has successfully detected sentinel nodes.[17] In more recent studies, acceptable lymphatic mapping and sentinel node biopsy have been reported during colorectal cancer resections performed through laparoscopy.[32] Sentinel node detection rates with the laparoscopic approach are successfully high without adding complexity or time to the surgical procedure. In fact, sentinel node biopsy will likely modify the resection limits in a significant number of patients, which may reduce chances of missing out nodes with tumor deposits.[32] Despite these encouraging results, several issues have to be dealt with, before lymph node sampling becomes a regular practice during laparoscopic resections for colorectal cancer. Radio-guided sentinel node detection technique has to be standardized, while more experience is gained to confirm accuracy and benefits of the procedure.

Biological significance of micrometastases detected by sentinel node biopsy

As surgery evolves, new approaches and management alternatives emerge for the treatment of gastrointestinal malignancies. Lymphatic mapping and sentinel node biopsy represents one of these advances and show great potential for improving the staging process of GI cancer. There is sufficient evidence in the literature that supports the use of the sentinel node concept for these tumors. However, many questions remain unanswered including the biological significance of micro-metastases in regional lymph nodes. Several ongoing clinical trials are addressing this important issue, and should in time provide the necessary information to judge the effect on survival, particularly if adjuvant therapy is to be offered based on the presence of micro-metastases that would otherwise have been missed out by routine lymph node histology.

Current knowledge indicates that upstaging GI cancer by sentinel node biopsy may increase the number of patients with nodal disease who can benefit with adjuvant chemotherapy.[6,28,30] Whether this enhanced staging can improve survival remains to be determined by prospective studies. In the mean time, evidence based on retrospective analysis show conflicting results.[33-35] Liefers at al. reported that detecting micro-metastases in regional lymph nodes is a prognostic factor for stage II colorectal cancer.[35] They also found that node negative patients, assessed by RT-PCR, showed better survival rates (91% *vs* 50%) compared to RT-PCR node positive patients.

It seems likely, then, that the combined use of sentinel node biopsy along with the molecular information obtained from the tumor provides a reliable predictor of survival and better prognostic information.[30]

Conclusion

Despite evident problems, such as skip metastases, which can be encountered in some GI neoplasms, most reported series suggest that lymphatic mapping and sentinel node biopsy is feasible. This technique has the potential to identify important nodes in the region of the tumor. Additionally, the focused analysis of harvested sentinel nodes can improve tumor staging. However, concern still persists regarding both validity of the procedure, and the biological significance of micro-metastases in regional sentinel nodes detected by multiple sectioning, RT-PCR and immunohistochemical staining.

Acknowledgment

We appreciate the kind contribution of *Science, Edition & Translation®* (robana@prodigy.net.mx), for editing this review paper.

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