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EDITORIAL

What's wrong with sentinel node mapping in colon cancer?

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Abstract

Despite near-universal embrace of the concept and clinical relevance of lymphatic mapping for sentinel node identification and analysis for cancers of the breast and integument, the same technique has struggled to a find a role in gastrointestinal cancers in general and, perhaps, in colon cancer in particular. Despite many studies demonstrating its feasibility in malignancies of the large bowel, concern is continually aroused by the variable and often unacceptably low sensitivity rates. Additionally, many confess uncertainty as to what benefit it could ever confer to patients even if it were proven sufficiently accurate given that standard surgical resection incorporates mesenteric resection anyway. However, the huge impact sentinel node mapping has had on clinical practice in certain cancers means that each of these aspects merit careful reconsideration, from very first principles.

Key words: Sentinel node; Lymphatic mapping; Colon cancer

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Despite being initially proposed many years before, the sentinel node concept has only recently impacted upon clinical practice. The major landmark work in validating the theory took place in melanoma patients[1], but the proof of the concept was quickly (and relatively painlessly) transferred to breast cancer[2]. However, perhaps the most salient aspect evident on reviewing these seminal publications now is their consistent focus on confining the technique to relatively early stage cancers. The rationale underlying this is that larger tumours involve a greater area of lymphatic channels and also that more advanced tumours may demonstrate aberrant lymphatic dynamics, both within the primary and in the lymphatic channels in the immediate vicinity. Lymphatic mapping is, therefore, currently recommended only for intermediate thickness melanoma (1.2 mm to 3.5 mm deep)[3] and T1 and 'early' T2 breast tumours[4,5]. As discussants of the topic with regard to colon cancer largely tend to overlook this basic tenet, it is worth reviewing the literature for *in vivo* sentinel node detection in colon cancer from this perspective (*ex vivo* work has been excluded from this review as it primarily is of interest from the point of view of pathological evaluation rather than surgical approach).

To date, there have so far been 37 publications in the English language describing over 2500 patients (although some studies may have overlapped their patient groups). Explicit cognisance of tumour advancement and mural penetration has mostly only been peripherally addressed in these studies, however, and tumour size hardly at all. Only four studies excluded patients with evident macroscopic lymphadenopathy[6-9] and it is interesting to note that each of these despite being relatively small studies from groups outside of the main proponent centres have excellent results given the other characteristics of their patient cohorts (see below). The authors with the most consistently impressive results have also tended to include relatively high proportions of "early tumours" (approximately 50% or more of their cancers have been T1 or T2)[2,5,10]. However, when collaborating in a multicentre study resulting in patients with tumours of somewhat more advanced T-stage, sensitivity rates reduced. Further examination of these patients led to the conclusion that this was primarily due to lymphatic obstruction by tumour[11]. Furthermore, when a related group described a cohort of somewhat more advanced primary tumours (at least in terms of T-stage) for the purposes of a different study their lymphatic mapping results also appeared worse (82% detection rate with 12% false negative rate) than those previously published[12]. Other authors have also reported high sensitivity rates when dealing with earlier tumours although this aspect of the patient demographic was not specifically teased out[13,14].

Conversely, the studies with the highest false negative rates have also tended to have the greatest proportion of T3/T4 tumours in their study cohorts (with the T3-T4 proportion representing at least two thirds of the total study group)[15-21]. Better results in such patient populations is reported in those studies which specifically excluded those with evident lymph node disease intraoperatively[9]. Of the studies that have considered any potential impact of T-stage, Viehl *et al*[22] found identification rates most significantly affected by tumour size:dye instillate ratio, Saha *et al*[23] found 95 per cent of so called 'skip metastases'

occurred in T3 and T4 tumours while Wood *et al*[24], Bilchik *et al*[25] and Kitagawa *et al*[26] all noted that their false negative cases occurred predominantly in T3/T4 patients. Furthermore, Ratanachaikanont *et al*[27] found significantly lower identification rates in these tumour categories and Yagci *et al*[28] documented lower sensitivities in those with advanced Dukes B cancers. The one exception to this very consistent trend has been the work of Paramo *et al*[29] who initially described a 0% false negative rate in their initial experience with predominantly T3 tumours. However, after further expanding their series (mostly by enlarging their numbers of T3 tumours), they found a 3% false negative rate[30] while, interestingly, neither report included any T4 cases.

Some other important studies have provided no meaningful details at all regarding T stage[31-39] and so do not lend themselves to be scrutinised in this fashion. However, given that they state no pre-selection criteria for their patients, it would seem likely that their patients were representative of typical presentation (which in the case of colon cancer is predominantly with transmural, node positive disease). Indeed, that the majority of studies include all comers in their validation studies is perhaps understandable given that most patients with potentially resectable tumours proceed to operation without particular consideration of tumour diameter or mural penetration. Nonetheless, inclusion of high proportions of more locally advanced tumours seems, both theoretically and empirically, to undermine the validation of the technique in this disease. While other factors such as operator experience and dye pharmacodynamics may, of course, also play a role, it would surely be of great interest to selectively, prospectively study sentinel node mapping in patients with early tumours. This would evidentially necessitate some means of preselection such as endoscopic ultrasound (proven efficacious in this tumour type as in other alimentary malignancies)[40] or by including for study only those with screen-detected cancers but would seem eminently feasible.

The second fundamental difference between SNM for cutaneous and breast tumours and that for colon cancer is in the overall intention of purpose. The fundamental principles ab initio diverge significantly, however, between the two as the intent of the technique when used in the former malignancies is to identify lymph node negative patients (in order to spare them from morbid lymph basin dissections) whereas in the latter it has focussed mainly on detecting lymph node positive patients (to identify those who have otherwise occult dissemination and who, therefore, could benefit from systemic therapy). Prognostic prediction (and, therefore, adjuvant therapy prescription) in colon cancer however is largely determined by lymph node involvement and recently much attention has focussed on the adequacy of nodal harvests (whether by surgeon resection or pathologist detection)[41]. It may well be, therefore, that the value of sentinel node identification and analysis is to confirm that lymphatic dissemination has not taken place in tumours likely to be of early stage in order to save the searching for sufficient numbers of nodes to prove this (in excess of 40 perhaps) that would otherwise be necessary[42]. From this viewpoint, the upstaging of some cancers that are conventionally node negative becomes an added bonus rather than the sole outcome to justify the effort involved. While such a hypothesis can obviously only be purely speculative at present, some proof of concept could perhaps be advanced by the early adopters of lymphatic mapping in colon cancer in examining the survival of their sentinel node negative patients to date in comparison to those deemed node negative by conventional means but with low nodal counts.

Finally, it is intriguing to question the widely held assumption that sentinel node mapping in colon cancer has no value in minimizing the operative morbidity associated with resection of colonic tumours[43]. This basic tenet has become so dogmatic that a sentence to this effect nearly always forms part of the introduction, discussion and/or accompanying editorials of publications concerning the topic[44]. The intent behind the standard operations performed for colonic cancer is, however, to achieve full lymph node basin clearance concomitantly with resection of the primary in every case ("en bloc" or radical resection). The fact that lymphatic drainage closely follows the arterial (rather then venous) regional blood supply is what prompts the level of proximal vascular ligation (a "high-tie") and it is this manoeuvre that then determines the extent of the segmental bowel resection required (in order to minimize the risk of ischemia of the residual bowel). In many cases, the magnitude of visceral resection provoked by radical lymphadenectomy is far in excess of what would be associated with curative surgery in terms of marginal clearance (colonic tumours rarely infiltrate more then 2 cm beyond the area of gross involvement and therefore a resection margin of 5-10 is considered appropriate)[45]. Although there is likely to be a therapeutic value in resecting nodes positive for metastatic disease in colon cancer, the main value of such clearance for truly lymph node negative patients can only be the gain of prognostic information for reassurance. If adoption of sentinel node mapping obviated the need for wide lymph basin clearance for intraperitoneal colon cancers, the potential benefits would include shortened operative times, reduced postoperative convalescence and, perhaps, improved bowel function[46] and diminished rates of anastomotic dehiscence[47]. Furthermore, the potential for ureteric, duodenal and (in the male) spermatic vessel injury would be greatly reduced if root mesenteric dissection became unnecessary as would the hazard of splenic laceration that occurs with mobilization of this flexure [often necessary after high ligation of the inferior mesenteric artery (IMA) to ensure tension-free anastomosis after radical left hemicolectomy for sigmoid tumours] and the risk of sexual impotence that may result if para-aortic nerve injury occurs during flush ligation of the IMA at its origin from the abdominal aorta. Lastly, if a localized resection of the bowel was all that was required, the facility by which excisional colonic cancer surgery is performed by minimally invasive means would be markedly enhanced (and the now arduous learning curve reduced). In short, the clinical significance of localized rather then

radical colectomy is not at present known, but cannot be assumed to be negligible.

The reasons why the basic principles regarding the validation and clinical utility of lymphatic mapping for colon cancer have become so fundamentally divergent from that of breast and melanoma is not entirely clear and, to date, have rarely been discussed. The simplest reason to suspect why it has occurred may be simply that the operative terminology has led to a prevailing mindset. As breast cancer surgeons always considered two operations for their patients (mastectomy/wide local excision and axillary node clearance) and melanoma surgeons always advocated wide excision and lymph basin dissection, perhaps the basic similarities would be easier appreciated if operations such as left hemicolectomy were to have more standardised names such as 'segmental colonic resection with mesenteric lymph node resection'.

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