II Série • N.º 10 • Setembro 2009

Revista Portuguesa de Cirurgia

II Série • N.º 10 • Setembro 2009

ISSN 1646-6918

Órgão Oficial da Sociedade Portuguesa de Cirurgia

Revista Portuguesa de Cirurgia

New horizons in colorectal cancer surgery

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Published online: 13 December 2008

Colorectal cancer is a major health problem. Worldwide, approximately 500,000 patients per year will die as a result of colorectal malignancy. The standard therapy is an adequate segmental resection en bloc with the adjacent lymph nodes. This can be performed by conventional open surgery or laparoscopic resection. Sufficient evidence has shown equal results in terms of lymph node harvesting, resection margins, and survival for both techniques. Local resection for rectal cancer in the early stages has been shown to be safe, despite the fact that the lymph node status cannot be established. Transanal endoluminal microsurgery (TEM) is an effective treatment for early rectal cancer. However, there has always been concern about the nodal status and the need for secondary surgery in case of lymphatic dissemination. Nodal involvement in TI tumors has been reported in up to 10%. With neoadjuvant radiochemotherapy, local resection and tumor control has been proven to be efficient. Some authors even consider local resection in early rectal cancer to be a superior therapy because of the huge impact on quality of life in case of rectal resection.

Imaging modalities, such as the USPIO MRI technique and PET scan technology, have improved the resolution to establish nodal involvement and preoperative staging, but pathological examination remains the "gold standard."

Colon cancer is diagnosed by endoscopic biopsies or polyp removal. In case of invading tumors additional adequate segmental colon resection with en bloc resection of lymph nodes is common, facilitated by tattooing. Today local resection for colon cancer is less attractive because of the restricted possibilities in neoadjuvant treatment modalities, such as local radiotherapy. and the minor implications in loss of functionality. Although sub mucosal resection of colonic neoplasia is being proposed as a sufficient therapy in selected cases, the uncertainty about the possible undetected concomitant lymph node metastases remains a serious drawback of the sub mucosal resection technique.

The sentinel node concept has been proven to be valid in many solid tumors. Since Morton et al. ^I] showed the validity of the concept in melanoma's and the subsequent identification of the SLN by lymphatic mapping in breast cancer by Krag et al. [21 and Giuliano et al. [31, the use of the SLN in the therapeutic strategy has altered profoundly the treatment of these cancers.

Similar to melanoma and breast cancer surgery with sentinel node biopsy, we speculate that local resection with SLN harvesting in early colon cancer might change the therapeutic and surgical strategy in colon cancer.

It has been shown that patients who are operated on with curative intent but who have lymph node metastases benefit from adjuvant chemotherapy in contrast to those without metastases.

Stage I and TI colorectal cancer implies no lymph node involvement: however, up to 30% of patients with stage I or II disease will develop locoregional recurrence or distant metastases and will eventually die from CRC. Therefore, standard surgery might not be sufficient in 30% of these patients. Some of these patients may recur because of hematogenous metastases, but a significant portion of these recurrences may occur due to the lack of detecting lymph node metastases, or aberrant lymphatic drainage beyond surgical margins.

The UICC recommend that a minimum of 12 lymph nodes must be evaluated in all surgically treated colon cancers [4]. The evaluation of 12 or more lymph nodes has been demonstrated to improve 5-year survival [5]. Vari-ability of both surgical technique and pathological harvest makes it difficult to standardize adequate lymph node identification.

Furthermore, advanced examination techniques will increase the likelihood of detecting occult tumor cells (OTC) or micrometastasis, such as serial sectioning, step sectioning, immunohistochemistry. polymerase chain reaction, and reverse transcriptase polymerase chain reaction. The disadvantages of these techniques are that they are time consuming and expensive.

The detection of the sentinel lymph node could be a solution for these problems by demonstrating the ability to increase lymph node harvesting and providing a limited number of sentinel lymph nodes in which OTC can he assessed. Despite the progress in recent years in the use and knowledge of sentinel node procedure in patients with colorectal cancer, we still face some problems that limit common use of the sentinel node technique.

Good results of sentinel node harvesting in colorectal cancers have been shown by large studies. In 2005 Saha et al. 16] published a multicenter trial that included 500 patients. In SLNM, patients' success, accuracy. sensitivity. and negative predictability values were *98`Ir. 96c4,* 90%. and 93°h-, respectively. For future studies it will he necessary to stratify patients according to their T stage. The sentinel node procedure is likely less reliable in advanced tumor stages. Another issue is the fact that a learning curve is probably necessary to obtain good results for SLNM. Also, the technique for the localization and the definitions of the sentinel node differ between studies (Table I). The following techniques have been used: only blue dye (in vivo or ex vivo), radioactive dye, and a combination of radioactive and blue dye or fluorescent dye (indocyanine ,green). To our knowledge, a comparative study between all these techniques has not been performed. Using the same definition and standardization of the SLNM procedure is

Table 1 **Definitions of the sentinel lymph node used in the literature**

A sentinel node is:

- Lymph node upon which the primary tumor directly drains
- Lymph node that is the nearest to the primary tumor Radioactive lymph node
- Most radioactive lymph node
- First lymph node found by lymphoscintigraphy
- Lymph node that has a certain factor higher radioactivity than the other lymph nodes or that of the local normal tissue
- Lymph node that is blue of color
- Lymph node that is visualized by infrared irradiation

mandatory to validate the sentinel node procedure for predicting the tumor status of all lymph nodes.

Another problem that we have to overcome is poor visualization of the tracer. The presence of mesenteric adipose tissue in patients with colorectal cancer makes is difficult to see the different kinds of ink. Also blue dye and indocyanine `green can readily diffuse through the sentinel node and transverse multiple nodes. The use of gamma tracers for SLNM in patients with colorectal cancer was first reported by Kitagawa et al. [7]: since then this technique has been used in different studies in combination with ink or as a tracer on itself. Even though the overall results do not show an additional value of the use of radioactive tracers, we think that the combination tech-nique is preferable. Saha et al. 181 published data that indicate

that a combination of isosulfan blue and a radio-active tracer may improve the identification, accuracy rate, and number of SLNs. In 2006 (our group) Terwisscha Van Scheltinga et al. [91 showed that in three patients (17[1-]/0 the positive SLN was detected by scintigraphy only and not with patent blue. Using a radioactive tracer alone presents the problem of signal interference of the injection site and a SLN situating near the tumor.

NEW HORIZONS

In 2003 Bilchik et al. [101 reported the feasibility of laparoscopic intraoperative lymphatic mapping with blue dye in 30 patients. The sentinel node analysis was shown to be efficient with *a 93r4c* accuracy rate. In 29% of patients unexpected lymph drainage altered the initial surgical procedure. Recently the group of Marescaux published a study of the sentinel node biopsy by Natural Orifice Transluminal Endoscopic Surgery (NOTES) technique [I 11. They localized and harvested successfully the sentinel node in six pigs by using, submucosal injection of methylene blue. In humans with a fatty mesentery. methylene blue, as said. might not he the preferred dye because of poor tissue contrast.

In 2006 Nagata et al. 1121 demonstrated successful laparoscopic sentinel node mapping using infrared ray laparoscopy (IRL) with indocyanine green staining. In 48 patients, IRL was shown to be five timers superior in localizing the SLN compared with conventional laparos-copy. As with methylene blue, indocyanine green also has disadvantages: it has poor penetration in fatty tissues (2-3 mm) and therefore is difficult to detect. Also. both dyes are small particles (<5 nm) and diffuse easily through lymphatic channels and (sentinel) lymph nodes.

The use of quantum dots (QD, nanocrystals with a metal shell and solubilizing organic coating), as published by Frangioni et al. 113], can enhance visibility because QDs are highly fluorescent. nonradioactive, and visible deep within tissue. Because of their size, QDs remain trapped in the lymph nodes. The unknown toxicity of the metals are restricting human use at present, although the doses used are far below (acute) toxic levels.

The use of a fluorescent dye conjugated with monoclonal antibodies, as published by Gutowski et al. [1T], could be significant in the future.

If we can enhance the fluorescent properties of the dye and bind them at malignant cells, it may he easier to detect the SLN. Also the intraoperative lymphatic mapping can reveal an aberrant lymphatic drainage as high as 30% [101.

CONCLUSIONS

Screening programs and increasing awareness of the symptoms of colorectal cancer will lead to increased numbers of detection of early-stage colon neoplasia with-out nodal involvement. The present standard surgical treatment may overtreat substantial numbers of patients who can benefit from local resection only and undertreat those who have lymphatic micrometastases. Despite the present difficulties in sentinel node lymphatic mapping in patients with colon cancer, minimal invasive detection and harvesting of the sentinel node will he important in future treatment of colonic neoplasia. The technique that is the most reliable for sentinel node detection has not yet been validated, however, the fluorescent technique seems very promising. Development of near-infrared devices for excitation and visualization of the fluorescent dyes will he necessary to optimize the potential of this technique.

Early colon cancers may be treated by local resection therapy only with a minimal invasive surgical sentinel node procedure. Similar to breast cancer surgery. these techniques may profoundly alter the way that we treat colon cancer, but only if the sentinel node can be detected and harvested in an accurate, safe. and reliable manner.

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