Review Article

Progress in sentinel lymph node in colorectal cancer

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ABSTRACT To understand sentinel lymph node (SLN) biopsy in colorectal cancer, we reviewed the current available literatures about the application of SLN biopsy in the field of colorectal surgery were collected and reviewed. In this article,we summarize the history, current status, methods and controversies of SLN biopsy,especially the significance of clinical application in colorectal cancer.SLN biopsy accurately detects the status of the nodal basin. Focused examination of the SLNs could identifies micrometastases that might be missed by routine histopathological analysis, thus upstaged this group of patients.SLN biopsy is a new and effective technique in predicting the tumor status of regional lymph nodes, which offers a potential alternative to improve the accuracy of tumor staging in colorectal cancer. However, further study is required.

Key Words: sentinel lymph node biopsy; rectum neoplasm; colon neoplasm; metastasis

What is Sentinel Lymph Node?

The first lymph node in the lymphatic basin draining the primary tumor is called the sentinel lymph node(SLN). If there is lymphatic spread of cancer it should involve the sentinel node first and then the other nodes. Sentinel lymph node biopsy(SLNB) technique accurately predicts the regional nodal status in colorectal cancer. The accuracy is higher than 96%.[1] The concept of 'sentinel lymph node' was first brought forward by Cabanas in 1977,when he studied patients with carcinoma of penis.[2] In 1988, Martin et al firstly applied SLNB technique to carcinoma in large intestine.[3] He not only predicted the extent of resection accurately, but also found the aberrant lymphatic metastasis. Both Saha et al and Bilchik et al demonstrated that the SLNB technique showed great promis in the staging of colorectal cancer, detection of aberrant lymphatic drainage, identification of micrometastasis and study of lymphatic metastasis mechanism in colorectal caner.[4-5] However, the application of SLNB in patients with colorectal cancer is still uncertain.

Localization of Sentinel Lymph Node

The sentinel lymph node can be identified using different methods. Though theoretically there should be only one node, usually more than one node is stained by blue dye or labelled with radiocolloid.

Isosulfan blue and nano-carbon black are frequently-used bioactive dyes in the detection of SLN. Staining methods are inexpensive, simple and free of radioactive contamination,but performance of dye injection and he SLN identification is required to be fast. ^{99m}Tc-sulphur colloid is often used in the radiocolloid method, which avoids widely damaging the tissue surrounding the rectum, decreases the false negative of SLN. The disadvantages of using radiocolloid are that it increases the radioactive contamination and requires enormous expenses and longer operation time. Most of time the above mentioned two methods are combined in detecting SLNB, which improves the detection rate of SLN, identification of micrometastases and upstaging of

The authors have no commercial,proprietary,or financial interest in the products or companies described in this article.

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colorectal cancer.[6] However, the operation is more complicated and the expense increases. Nanotechnological quantum dots(QD) is a new method for SLN mapping , which is free of radioactive contamination and accurately localizes the SLN.[7]

SLN was localized during the surgery in patients with colorectal cancer. The tracer agent was injected into the subserosa around the tumor before resection to seek SLN. A gentle massage was given for 10-15 minutes to facilitate the drainage of dye to lymph nodes. The intraoperative localization method is simple and accurate,which is beneficial to definition of resection extent,identification of unexpected drainage route and accurate postoperative staging. Its disadvantages are that the operation time is extended by 10~15 min and thus the dissemination of tumor cells is inevitable. Overall, the intraoperative localization method is feasible to identify the SLN in patients with colorectal cancer. Postoperative localization of sentinel lymph node is to inject tracer agent 30 min after the tumor resection to localize the SLN. Its advantages are as follows: 1) easy to operate and reduce postoperative complications; 2) to avoid the tumor cells dissemination; 3) to avoid the tracer-relative adverse reaction; 4) confided to pathologist to identify the micrometastasis,improve the detection rate and modify the nodal staging;5) a supplement to failure of intraoperative method.8 But postoperative lymphatic drainage does not meet the physiological characteristics, and the aberrant lymphatic drainage would be missed. However, Fitzgerald et al reported that the postoperative localization method was feasible in 30 min after the resecion.[9] Bilchik et al used both intraoperative and postoperative methods to localize the SLN in patients with colorectal cancer. He demonstrated that the two methods had no significant difference in detection rate, mean SLN,and the accuracy, which suggested that the two methods were both feasible for detection of SLN in colorectal cancer.[10]

Pathological Examination

SLN could reflect regional nodal statu,and its quantity is less,so it is worth a detailed pathological examination. The common methods are as follows:1)Hematoxylin and eosin (HE) staining staining is the most commonly used method,which detects most tissue of the lymph node, but might miss the nodal micrometastasis. 2)Immunohistochemistry (IHC) using cytokeratins20 is more sensitive than HE in detecting the nodal micrometastasis because cytokeratins20 is a sensitive and specific tumor maker for large intestine carcinoma micrometastasis. 3)Reverse transcriptase- po1ymerase chain reaction (RT-PCR) identifies the micrometastasis by amplifying the mRNA expressing in tumor tissue but not in the normal tissue. RT-PCR has high sensitivity and specificity, which is expected to be a routine method in detecting SLN.[11] 4)DNA mutation detection and micropartical enzyme-linked of immunosorbent assay(MEIA) are both uncommon because they are expensive and complicated.

Significance of Sentinel Lymph Node

SLN detects the nodal micrometastasis. In 1992, Union for International Cancer Control (UICC) defined micrometastasis as a single metastatic tumor cell or cell mass whose diameter was less than or equal to 2 mm.[12] The HE staining of micrometastasis is negative, while the IHC result is positive. The routine examination of lymph node is to dye a single slice of each node by HE and then observe it under the optical microscope,which might miss the nodal micrometastasis and result in down-staging. Kelders multicenter clinical trial demonstrated that 18 percent of colon cancer patients had micrometastases.[13] Serial section technique, IHC and RT-PCR detect the micrometastasis and upstage the tumor.[14-15] Prophylactic chemotherapy to all patients with colorectal cancer is impracticable and inadvisable. The prognosis of patients in stage Ⅲ was bad and adjuvant chemotherapy should be recommended. Lymph node-negative patients had higher survival rate,so adjuvant chemotherapy was not recommended. SLNs can reflect the regional nodal status and get an exact staging. Quadros et al found that upstaging benefits of SLN mapping should be considered in colon and mid- and upper rectal tumors. The method should be avoided in patients with lower rectal tumors, large tumors and having had neoadjuvant therapy.[16]

SLN indicates aberrant lymphatic drainage. Bilchik et al found that SLN can be far away from the primary tumor.[17] Aberrant lymphatic drainage(ALD) means that SLN is found outside the lymph node basin. Andreas et al reported that 1.6 percent of 315 patients with colon cancer had ALD.[18] ALD-lymph node might be the only metastatic one. The resection depends mainly upon the site and size of primary tumor. Selective clearance of lymph nodes is not recommended at present. On the contrary, extended lymphadenectomy is necessary in patients with ALD. Saha et al demonstrated 11 of 198 patients enlarging the resection extent due to ALD improved cure rate.[1]

SLN promoted the development of minimal invasive surgery. On one hand, with the advent of minimal invasive surgery, laparoscope is applied to colorectal neoplasm. SLNB is a reference in judging whether the tumor could be resected by laparoscopic surgery. On the other hand, due to the development of endoscopy and endoscopic ultrasonography, detection rate of early cancer increased year by year. SLNB confirms reasonable extent of lymphadenectomy without extensive injury of pelvic nerves which may result in urinary retention and sexual

dysfunction. However, large sample and prospective case-control clinical trials are required to confirm the feasibility.

SLN lightens the burden both of pathologists and patients. Wong et al thought at least 14 lymph nodes were neseccery to predict the regional nodal status.[19] Generally 4~52 lymph nodes can be identified from each specimen of colorectal cancer. Routine histopathology might neglect micrometastases, while serial sections, immunohistochemistry or RT-PCR to each lymph node would increase the work of pathologists and the financial burden of patients. In general,1~4 sentinel lymph nodes can be identified from each patient. The sensitivity and specificity of SLN pathologic examination are higher. More accurate staging can be obtained by a detailed examination to routine pathological examination-negative SLN. Hence, SLNB saves a lot of resources and have high feasibility and practicality.

SLNB is helpful in discovering the mechanism of lymph metastasis in colorectal cancer. The mechanism of tumor cells leaving from primary focus, invading lymphatic vessels and metastasizing to regional lymph nodes is complicated. Lymph node metastasis is closely related to lymphatic vessel invasion. With the development of molecular biology, specific markers of lymphatic endothelial cell such as VEGF-C and VEGF-D have been found. VEGF-C or VEGF-D combines with their receptors in lymphatic endothelial cells, inducing proliferation and growth of new lymphatic capillaries. Lymphangiogenesis may be a key step in tumor lymphatic metastasis.[20] It has been reported that chemokine receptor CXCR4/CXCL12 is highly expressed in primary colorectal cancers and metastatic lymphatic tissues. CXCR4 signal transduction pathway may play an important role in lymphatic metastasis in colorectal cancer.[21] Lymphangiogenesis inhibitor and SLN mapping as a study method for tumor lymphatic metastasis mechanism may offer a new approach for colorectal cancer treatment.

The Controversies on the SLN

Although SLB has shown great promising, the clinical impact of SLNB in colorectal cancer is still controversial.[22] 1) SLNB techniques were not consistent:Due to the fact that different methods were used ,such as the tracer agent, injection site, injection time, SLN detection technique, the histopathological examination and so on, a definite conclusion cannot be drawn. 2) SLNB is not suitable for all colorectal cancer patients. Patients with recurrent colorectal cancer,local metastasis,lymphatic tissue injury or preoperative radiotherapy should not be treated with SLNB. 3) Lymphatic metastasis is a main way of colorectal cancer metastasis,but not the only one. Patients without regional lymphatic metastasis may have distant metastasis. 4)The false-negative rate is high, which may be relevant with anatomy,pa thology,physiology,technology and so on. 5)SLNB is operator dependent,which results in individual difference.

Conclusion

In colorectal cancer patients, SLN can be used to predict the regional nodal status,which is an exciting new tool for accurate staging,resection extent and individual therapy. But the contribution of SLNB to colorectal cancer patients is still unspecified. Further large multicentric prospective trials are required to draw further conclusion.

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