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SUGGESTION OF OPTIMAL PATIENT CHARACTERISTICS FOR SENTINEL LYMPH NODE MAPPING IN COLORECTAL ADENOCARCINOMA

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ABSTRACT – ***Context*** - In a previously published study, the variables lower rectal tumor site, preoperative chemoradiotherapy and large tumors were considered as independent risk factors for the inability of sentinel lymph node identification in patients with colorectal adenocarcinoma. ***Objectives*** - To determine if these variables could interfere in the precision and upstaging benefit of sentinel lymph node mapping in colorectal cancer. ***Methods*** - A database composed of 52 patients submitted to lymphatic mapping using technetium-99m-phytate and patent blue was reviewed. Only patients with tumors smaller than 5.0 cm, not submitted to preoperative chemoradiotherapy and without lower rectal cancer were included. ***Results*** - With these parameters, 11 patients remained to be studied. The sentinel lymph node identification rate was 100%, with a sensitivity of 100%, negative predictive value of 100%, no false negatives and accuracy of 100%. Sentinel lymph nodes were the only metastatic nodes in 36.4% of the patients, micrometastases (<0.2 cm or only identified by immunohistochemistry) provided an upstaging rate of 27.1% and metastases an upstaging rate of 9.1%. ***Conclusion*** - The parameters proposed in this study for selection of colorectal adenocarcinoma patients to be submitted to sentinel lymph node mapping identified optimal accuracy and good upstaging results. As the number of included patients was low, these results could serve as guidance for proper patient selection in further prospective lymph node mapping studies in colorectal cancer patients.

HEADINGS – Colorectal neoplasms. Adenocarcinoma. Neoplasm staging. Sentinel lymph node biopsy.

INTRODUCTION

Sentinel lymph node mapping – SLNM has been advocated for improving cancer staging in colorectal adenocarcinoma patients. Radioactive markers and blue dyes are injected around the tumor and used as lymphatic tracers, as standard colorectal surgery is performed and up to five lymph nodes are identified by the tracers and retrieved as sentinel lymph nodes. The aim of SLNM is to identify metastatic lymph nodes in a direct drainage pathway from the tumor's lymphatic basin. Performing SLNM during standard colorectal surgery provides the retrieval of a small number of sentinel lymph nodes that represent the entire surgical specimens' lymph node status. A more detailed pathologic examination of the sentinel lymph nodes results in the detection of lymph node metastases that otherwise would go undetected, improving nodal staging[10].

Our previous publication described the results of 52 consecutive colorectal adenocarcinoma patients who were submitted to SLNM performed with technetium-99m-phytate and patent blue dye during their standard curative surgery. The study's multivariate statistical analysis considered lower rectal tumor site, preoperative chemoradiotherapy (neoadjuvant treatment) and large tumors as independent risk factors for the inability of sentinel lymph node identification[10].

The study database was reviewed, assuming that the three variables implicated in the inability to identify sentinel lymph nodes, could interfere with the accuracy and upstaging benefit of SLNM. The aims of this study were to evaluate the accuracy and upstaging benefits of the sentinel lymph node procedure when the variables lower rectal cancer, neoadjuvant treatment and large tumors were excluded from the database.

METHODS

SLNM using technetium-99m-phytate and patent blue was performed prospectively in 52 consecutive colorectal adenocarcinoma patients during their standard curative surgery, from January 2004 to July 2005[10]. All surgical procedures and pathologic examinations were performed respectively by the first and third authors, at a single institution, the Aristides Maltez Hospital, Salvador, BA, Brazil. Local and national ethics committees approved the trial, and

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written informed consent was obtained from all patients. Patient inclusion criteria in the study were absence of distant metastases identified in preoperative or intraoperative evaluation and resection of the primary colorectal cancer with curative intent.

The neoadjuvant chemoradiotherapy protocol, SLNM procedure, and the special methods for enhanced pathologic analysis including step-sectioning and immunohistochemistry were described in a previous publication[10]. The definition of micrometastasis was nodal tumor measured less than 0.2 cm in the larger diameter or only detectable by immunohistochemistry. Micrometastases were considered in the SLNM upstaging benefit[12]. Patient staging was performed accordingly to the Tumor, Nodal, Metastasis – TNM cancer staging manual[5]. Colon and sigmoid colon cancers were analyzed together as they share similar mesentery and lymphatic chain characteristics. Rectal cancers were defined as tumors originating at or below the peritoneal reflection. The rectum was divided into three anatomic regions. The upper rectum was the proximal 1/3 starting at the peritoneal reflection. The lower rectum was considered the lower 1/3 including the anal canal. The mid-rectum was the intermediate 1/3 rectal segment between the upper and lower rectum[10].

Information obtained from the prospective study of the identification of sentinel lymph nodes in 52 colorectal cancer patients was organized in a database that was part of a previous publication. Multivariate statistical analysis had identified independent risk factors related to the inability to identify sentinel lymph nodes. These variables were lower rectal tumor site ($P = 0.009$), neoadjuvant treatment ($P = 0.029$) and tumor size (large tumors) ($P = 0.036$). In the present study, it was postulated that these three variables were related not only to the inability to identify sentinel lymph nodes, but that they might have also been responsible for influencing negatively SLNM accuracy and upstaging benefit. To test this hypothesis, the database that originated the previously published study was retrospectively analyzed excluding the variables lower rectal cancer site, neoadjuvant treatment and large tumors[10]. Large tumors were defined as tumors with one of its diameters larger than 5.0 cm. Accuracy tests and upstaging caused by SLNM were analyzed in the patients remaining in the database.

The accuracy of lymphatic mapping in colorectal cancer lymph node staging was evaluated using the following statistical measures described by Saha et al.[12]. The identification rate was calculated as the number of lymphatic mapping procedures where at least one sentinel lymph node was identified, divided by the total number of procedures attempted. True positives (TP) were defined as the cases where sentinel lymph nodes had metastatic cells whether or not metastatic cells were found in other nodes. True negatives (TN) were the cases where neither sentinel nor nonsentinel lymph nodes had metastatic cells. False negatives (FN) were defined as cases where the sentinel lymph nodes were negative whereas the nonsentinel nodes were positive. The equations of the variables are demonstrated as follows: sensitivity was calculated using the formula TP/(TP+FN), false negative as FN/(FN+TP), negative predictor value as TN/(FN+TN) and accuracy as (TP+TN)/(TP+FP+FN+TN)[10, 12].

RESULTS

SLNM in the 52 colorectal adenocarcinoma patients had an identification rate of 75% (39/52). The accuracy of the method for correct nodal staging was 79.5%. Sensitivity was of 65.2%, negative predictive value was 66.7% and false negatives were 34.8% (Table 1).

TABLE 1. Identification rate and accuracy of sentinel lymph node mapping with technetium-99m-phytate and/or patent blue dye in adenocarcinoma colorectal patients

	Entire group	Reviewed database*
Total number of patients	52	11
Identification rate	75% (39/52)	100% (11/11)
Accuracy rate	79.5% (31/39)	100% (11/11)
Sensitivity	65.2% (15/23)	100% (11/11)
Negative predictive value	66.7% (16/24)	100%
False negatives	34.8% (8/23)	0
Patients upstaged	23.1% (9/39)	36.4% (4/11)
Metastasis upstaging**	7.7% (3/39)	9.1% (1/11)
Micrometastasis upstaging***	15.4% (6/39)	27.3% (3/11)

* Reviewed database, excluding patients submitted to preoperative chemoradiotherapy, with lower rectal cancer and with tumors larger than 5.0 cm

** Patients upstaged by metastasis ≥0.2 cm in greatest dimension

*** Patients upstaged exclusively by micrometastasis (<0.2 cm in greatest dimension) or by immunohistochemistry

Patients with the variables lower rectal cancer site and neoadjuvant treatment, as well as tumors larger than 5.0 cm, were excluded from the database. With these new parameters, 11 patients remained to be studied, 6 with colon tumors and 5 with rectal tumors. An analysis was carried out with the data provided from the SLNM procedures performed in these 11 patients. The sentinel lymph node identification rate was 100% (11/11), with sensitivity of 100%, negative predictive value of 100%, no false negatives, and accuracy of 100%.

Sentinel lymph nodes were the only metastatic nodes in four patients, upstaging 36.4% of the studied patients. In these four patients, in which metastases were present only in the sentinel lymph nodes, micrometastases were responsible for the upstaging of three patients (upstaging rate of 27.1%) and metastases were present in one patient (upstaging rate of 9.1%) (Table 1).

DISCUSSION

The presence of lymph node metastasis is the most important prognostic factor in colorectal adenocarcinoma and indicates adjuvant chemotherapy[8]. In colorectal cancer, SLNM aims to increase the detection of lymph node metastasis without modification of the standard surgical procedure[10]. The procedure permits a substantial upstaging benefit in patients with colorectal adenocarcinoma, indicating chemotherapy in patients that would otherwise not be submitted to adjuvant treatment[10, 12]. In colorectal cancer, the procedure aims to increase the detection of lymph node metastasis without

modification of the standard surgical procedure. Lymph node metastases are identified in sentinel lymph nodes by enhanced pathologic examination in patients who would be considered node negative if only conventional pathologic evaluation was performed[10]. Data from all publications of SLNM in colorectal cancer, despite the low accuracy results of some series, demonstrate that the percentage of patients classified erroneously as TNM stage II[5] could be reduced with the incorporation of the identification of sentinel lymph nodes[10]. This upstaging benefit achieved with SLNM contributes to patients' oncological treatment as chemotherapy has the potential of reduction mortality in up to 33% in colorectal adenocarcinoma patients with lymph node metastasis[13].

Saha et al.[12] demonstrated a 14.8% increase in lymph node metastasis detection when patients submitted to resection of colorectal tumors with SLNM are compared to patients that are operated without the use of the procedure (49.5% versus 34.7%; $P \leq 0.001$). Patients in the same center were submitted to curative surgery for the treatment of colorectal cancer and evaluated as two groups. One group consisted of 153 patients in whom the identification of sentinel lymph nodes was performed (group A), the other group was composed of 162 patients in whom the procedure was not carried out (group B). These patients were followed-up for a minimum of 2 years with a median of 5 years. In patients considered lymph node negative and not submitted to adjuvant treatment, the rate of recurrence was 3% in group A and 18% in group B ($P = 0.002$). The difference found between the groups in terms of detection of lymph node metastases (14.8%) is similar to the difference in recurrence rates in patients considered node negative (15%). The greater recurrence rate of node negative patients in group B can be attributed to the erroneous designation of TNM stage II in patients with lymph node metastases not detected by conventional histopathological examination, where chemotherapy is not offered to these patients[5, 12].

Studies have suggested, without evidence of statistical significance, poorer SLNM results in colorectal cancer patients with large tumors and advanced disease[2, 7] also in patients submitted to preoperative chemoradiotherapy[11]. But there is still necessity of defining precisely the optimal patient characteristics for performing SLNM in colorectal adenocarcinoma. In a previously published study, we demonstrated, with multivariate statistical analysis, that in patients submitted to neoadjuvant chemoradiotherapy, with lower rectal cancer and large tumors, the identification of sentinel lymph nodes was not feasible[10]. The present study demonstrates that when these variables are excluded from the database, SLNM satisfactory accuracy results and upstaging benefits are obtained. This fact suggests, in the patients included in this study, that the variables preoperative chemoradiotherapy, lower rectal tumors and tumors larger than 5.0 cm were not only responsible for a deficient migration of the tracers patent blue and technetium-99m-phytate, but also interfered with the accuracy and upstaging benefit of the SLNM procedure. When patients with these variables are excluded from the database analysis, optimal accuracy and upstaging benefits are achieved.

There has been current concern about proper selection of tracers, injection methods and pathological protocols in colorectal SLNM. But, reviewed English written studies have not suggested a precise definition of optimal colorectal cancer patient's characteristics for SLNM[1]. The present study suggests that the selection of colorectal cancer patients' characteristics to be submitted to SLNM may lead to an excellent accuracy rate and better upstaging benefit. The lack of standardization of the SLNM procedure results in different study group characteristics, resulting in heterogeneous accuracy[10]. Sensitivity has been revealed to be as low as 38%[4] and as high as 100%[9], with identification rates ranging from 58%[3] to 100%[7] and false negatives from 0%[7] to 60%[6]. A precise definition of patients to be submitted to SLNM might also affect positively in the method's upstaging rate. The upstaging rate provided by the sentinel lymph nodes identification in this study was better than the 26.1% rate achieved in the largest multicenter SLNM study[12].

There have not yet been defined what colorectal cancer patients benefit the most from SLNM[1]. The optimal patient characteristics for SLNM identified in this study are those with small colorectal tumors, not submitted to preoperative chemoradiotherapy, and without lower rectal cancer. Since only 11 patients were studied, further prospective SLNM studies should be conducted to validate the results presented here, including patients with the optimal characteristics proposed in this study.

CONCLUSION

The parameters proposed in this study for selection of colorectal adenocarcinoma patients to be submitted to SLNM identified optimal accuracy and good upstaging results in the 11 studied patients. As the number of included patients in this study was low, it is suggested that the validation of these results be carried out with future prospective studies.

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RESUMO – ***Contexto*** - As variáveis tumor de reto inferior, quimiorradioterapia pré-operatória e grandes tumores foram considerados fatores de risco independentes para a inabilidade de identificação de linfonodos sentinela em pacientes com adenocarcinoma colorretal. ***Objetivos*** - Determinar se essas variáveis poderiam interferir na precisão e no aumento do estádio proporcionado pelo uso da técnica de identificação de linfonodos sentinela em câncer colorretal. Revisão da precisão da técnica do estádio foi realizada. ***Métodos*** - O banco de dados composto por 52 pacientes submetidos a mapeamento linfático usando tecnécio-99m-fitato e azul patente foi revisado. Foram incluídos somente pacientes com tumores menores que 5,0 cm, não submetidos a quimiorradioterapia pré-operatória e sem tumores de reto inferior. ***Resultados*** - A taxa de identificação de linfonodos sentinela foi de 100%, com sensibilidade de 100%; valor preditivo negativo de 100%, não houve falso-negativos e a precisão foi de 100%. Os linfonodos sentinela foram os únicos linfonodos metastáticos em 36,4% dos pacientes; micrometástases (<0.2 mm ou somente identificadas com imunoistoquímica) proporcionaram taxa de aumento no estádio de 27,1% e metástases taxa de 9,1%. ***Conclusões*** - A validação dos resultados deste estudo deve ser realizada em estudos prospectivos de identificação de linfonodos sentinela que incluam pacientes com câncer colorretal com as características propostas.

DESCRITORES – Neoplasias colorretais. Adenocarcinoma. Estadiamento de neoplasias. Biopsia de linfonodo sentinela.

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