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Original article

The clinical importance of micrometastases within the lymphatic system in patients after total gastrectomy

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ABSTRACT

Background: In spite of radical gastrectomy with resection of the lymphatic system, where no metastases are found during histopathological examination, about 30% of patients have relapse of the neoplastic process. This situation may be caused by micrometastases or isolated neoplastic cells in the lymphatic system which were not identified during a standard histopathological examination.
Aim: The aim of the study was to evaluate the clinical importance of micrometastases within the lymphatic system in patients with gastric cancer.
Materials and methods: A group of 20 patients treated for gastric cancer were subjected to retrospective analysis. Of all the patients who underwent surgery, a group with tumours classified as T1 or T2 was selected. No metastases within the lymphatic system were found in the standard evaluation – N0 mark. Paraffin-embedded blocks of lymph nodes were cut and new specimens were made, which were then stained again by means of immunohistochemistry. Antibodies against cytokeratin AE1/AE3 were used.
Results: A total of 319 lymph nodes were assessed in 20 patients in an H+E examination. After the immunohistochemical examination, micrometastases within the lymphatic system were found in 4 (20%) patients and isolated neoplastic cells in other 4 (20%) patients.
Conclusion: On the basis of numerous publications and our own material, we think that the presence of micrometastases may be related to a worse prognosis. The clinical importance of micrometastases within the lymphatic system in patients after total gastrectomy.

1. Background

The incidence of gastric cancer in Europe and Poland shows a falling tendency. Nevertheless, gastric cancer continues to be a significant clinical problem. It is the second malignancy causing most deaths around the world.[1] The results of treatment of advanced gastric cancer are unsatisfactory and leave much to be desired.

In patients with gastric cancer, the most important prognostic factor is the state of the regional lymphatic system. In spite of radical gastrectomy with resection of the lymphatic system, where no metastases are found during a histopathological examination, about 30% of patients have

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relapse of the neoplastic process.[2] This situation may be caused by micrometastases or isolated neoplastic cells in the lymphatic system, which were not identified during a standard histopathological examination. A standard procedure is to subject a lymph node to section in one plane and to collect two or three specimens, which are subsequently stained with haematoxylin and eosin. Small concentrations of gastric cancer cells located in the subcapsular sinuses of lymph nodes may be overlooked during a standard histopathological evaluation. The application of more sensitive methods of histopathological evaluation such as immunohistochemical examination or molecular biology techniques enables identification of micrometastases and isolated tumour cells within the lymphatic system, which were not found during a standard evaluation. Similarly, in the case of other tumours such as: breast cancer, melanoma, lung cancer or colorectal cancer, the application of immunohistochemical staining for evaluation of the lymphatic system enables identification of micrometastases in up to 20–45% of patients on average.[3–5] At present, there is no definite opinion concerning the importance of micrometastases within the lymphatic system.

2. Aim

The aim of the study was to evaluate the clinical importance of micrometastases within the lymphatic system in patients with gastric cancer.

3. Material and methods

A group of 20 patients treated for gastric cancer at the Department I of General Surgery and Surgical Oncology, Greater Poland Cancer Centre, Poznań, Poland, from 2002 to 2007 were subjected to a retrospective analysis. All consecutive, eligible patients treated in this period were enrolled for the study. No patient received neoadjuvant or adjuvant therapy. On the basis of prior diagnosis of adenocarcinoma, all the patients underwent total gastrectomy with resection of the lymphatic system, inclusive the second compartment (D2 resection). The continuity of the alimentary tract was reconstructed by means of the Roux-Y method. After the surgery, all the patients underwent a standard histopathological evaluation of the entire resected specimen. The evaluation of the lymphatic system consisted in the section of the node and collection of one or two specimens. After fixing, the specimens were stained with haematoxylin and eosin and then subjected to microscopic assessment. Of all the patients who underwent surgery, a group with tumours classified as T1 or T2 was selected. No metastases within the lymphatic system were found in the standard evaluation – N0 mark. Paraffin-embedded blocks of lymph nodes were excised and new specimens were made, which were then stained again by means of immunohistochemistry. Antibodies against cytokeratin AE1/AE3 were used. The obtained specimens were assessed by a histopathologist. According to the definition, the cellular deposits with diameter range between 0.2 and 2 mm were recognised as micrometastases. On the other hand, the concentrations of neoplastic cells with the diameter smaller than 0.2 mm were recognised as isolated tumour cells.

4. Results

A total of 319 lymph nodes were assessed in 20 patients in an H+E examination, i.e. 15.96 nodes per patient, median 15.5. After the immunohistochemical examination, micrometastases within the lymphatic system were found in 4 (20%) patients and isolated neoplastic cells in other 4 (20%) patients. Thus, the application of the immunohistochemical examination enabled identification of neoplastic cells within the lymphatic system in 8 (40%) patients (Table 1). In all the patients with diagnosed micrometastases, tumour was located subcardially and the micrometastases were found in the lymph nodes around the cardia, i.e. groups 1 and 2 in the Japanese classification. In two of the four patients apart from the micrometastases there were isolated tumour cells identified in another nodal station along the lesser curvature station 3. The survival time of the patients with identified micrometastases was lower than that of the patients without neoplastic cells found within the lymphatic system after immunohistochemical examination. It was 34.69 months vs. 49.86 months, respectively. In the case of isolated neoplastic cells located in the lymphatic system, in comparison with the N0 group after immunohistochemical examination, the difference in survival time was 45.33 vs. 49.86, respectively. On the other hand, in the group of patients with identified micrometastases, the survival time was shorter in the patients with isolated tumour cells identified in other nodal stations besides the micrometastases, i.e. 16.15 months vs. 53.22 months. The statistical analysis was not performed due to the group of patients being too small.

5. Discussion

Radical resection of the whole organ together with the lymphatic system still remains a standard method of treatment of gastric cancer. Unfortunately, even as much as 13.8% of patients who underwent radical resection due to early gastric cancer infiltrating only the mucosa or submucosa have a relapse of the neoplastic process. In a multi-factor analysis of the causes of relapse of early gastric cancer, which comprised a group of 3883 patients, Youn et al. recognised the following negative risk factors: age, size of tumour, number of focuses and state of lymph nodes. Of the elements listed above, it was the state of the regional lymphatic system that proved to be the most significant factor of relapse. In the group subjected to analysis, the most frequent occurrences were: the formation of distant metastases (55.7%), local relapse (34%) and invasion of the peritoneum (10.3%).[6] Lai et al. presented similar conclusions on the basis of an analysis of 2923 patients with early gastric cancer. The authors regarded the presence of metastases in the lymphatic system to be the first independent risk factor of relapse of the neoplastic process.[7] It is very likely that relapse of the neoplastic process is caused by unidentified micrometastases of the gastric cancer which are present in the lymphatic system.