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Identification of the sentinel lymph node in patients with colorectal cancer – preliminary report

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Introduction. Lymph node involvement is a very important prognostic factor in patients with colorectal cancer. The authors have undertaken an attempt to identify the sentinel lymph node (SN) in this clinical entity in order to evaluate the role of this method in defining disease advancement and its impact on treatment planning and prognosis
Material and methods. The study was performed on 41 pts with microscopically confirmed colorectal cancer. The sentinel node was identified with dye in 41 pts, and immunohistochemically in 17 pts.
Results. The SN was identified in 95% of pts with cancer of the colon and in 62% of pts with cancer of the rectum. In 19 pts we found no metastases in the SN nor in the other regional lymph nodes (RLN). In 3 pts the SN was the only node to contain metastases. In 16 pts we found metastases both in the SN and in the RLN, while in 3 pts the SN contained no metastases while they were present in other RLN.
Summary. All pts underwent resection of the colon and of the regional lymph nodes. The query concerning the indications for adjuvant chemotherapy in patients with confirmed micrometastases to the SN remains an open issue.

Zastosowanie techniki oznaczania węzła „wartownika" w raku okrężnicy i odbytnicy – doniesienie wstępne

Wstęp. Bardzo ważnym czynnikiem rokowniczym w raku jelita grubego jest obecność przerzutów nowotworowych w węzłach chłonnych. Autorzy podjęli próbę zastosowania oznaczania węzła „wartownika" (WW) w nowotworze o tej lokalizacji w celu oceny przydatności omawianej metody w ustalaniu stopnia zaawansowania, wpływu na planowane leczenie skojarzone oraz rokowanie.
Materiał i metoda. Badaniu poddano 41 pacjentów z rozpoznanym mikroskopowo rakiem jelita grubego. Do oznaczenia węzła wartownika zastosowano metodę barwnikową u 41 pacjentów oraz metodę immunohistochemiczną u 17 pacjentów.
Wyniki. W badanej grupie chorych w przypadku raka okrężnicy oznaczono WW u 95% badanych, zaś w raku odbytnicy u 62% badanych. U 19 chorych nie stwierdzono przerzutów do WW, ani innych regionalnych węzłów chłonnych (RWC). U 3 chorych WW był jedynym węzłem zawierającym przerzuty. U 16 chorych stwierdzono przerzuty do WW i RWCU 3 pacjentów stwierdzono przerzuty tylko do RWC przy braku przerzutów do WW.
Podsumowanie. Wszyscy pacjenci zostali poddani zabiegowi operacyjnemu, polegającemu na resekcji jelita i usunięciu regionalnego układu chłonnego. Ustalenie wskazań do chemioterapii uzupełniającej u pacjentów ze stwierdzonymi mikroprzerzutami tylko do WW jest nadal sprawą otwartą.

Słowa kluczowe: rak okrężnicy, rak odbytnicy, węzeł chłonny „wartownik"
Key words: colon cancer, rectum cancer, sentinel lymph node

Introduction

The incidence of colorectal cancer continues to increase. In 2001 coleractal cancer was the second most common malignancy in the Polish populace with 10 000 new cases registered. Similar tendencies may be observed in other developed countries [1, 2].

In Poland 5-year survival of patients with cancer of the colon reaches 31.6%, while with cancer of the rectum

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– 28.6%. In the United States these values are better by half – 59% and 57%, respectively [2].

Disease advancement is one of the most important prognostic factors. The study which we have performed was concerned with the identification and evaluation of the sentinel lymph node (SN) and was aimed at resolving the question whether immunohistochemical examination will increase the number of recognized micrometastases, and thus increase the number of indications for adjuvant chemotherapy.

Material and methods

Between June 2002 and February 2004 we had attempted to identify and analyze the sentinel lymph node in 41 patients with colorectal cancer (25 pts with cancer of the colon and 16 pts with cancer of the rectum) treated surgically at the Clinic of Oncological Surgery of the Medical Academy in Gdańsk.

The patients entered the study only if the regional lymph nodes were found not to be enlarged in USG and CT of the abdomen and on macroscopic intraoperative evaluation. (TNM advancement stage I and II).

Mean patient age was 67 yrs (range: 49-84 yrs). In all patients with cancer of the colon we performed resection of the colon together with the tumour and the regional lymph nodes (right hemicolectomy in 6 cases, left hemicolectomy in 7 cases, sigmoidectomy in 12 cases). Of the 16 pts with cancer of the rectum 9 underwent rectal amputation (modo Miles) and 7 – anterior resection (modo Dixon).

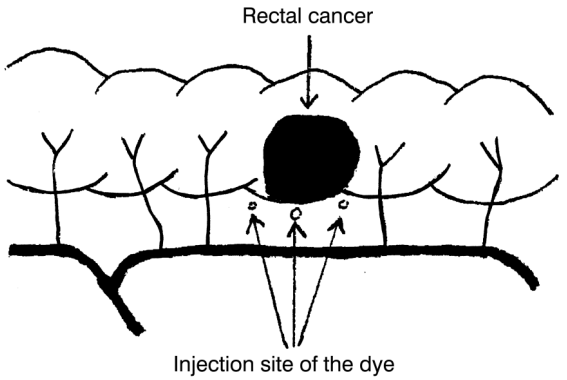

Figure 1. The technique of sentinel lymph node identification in patients with cancer of the colon

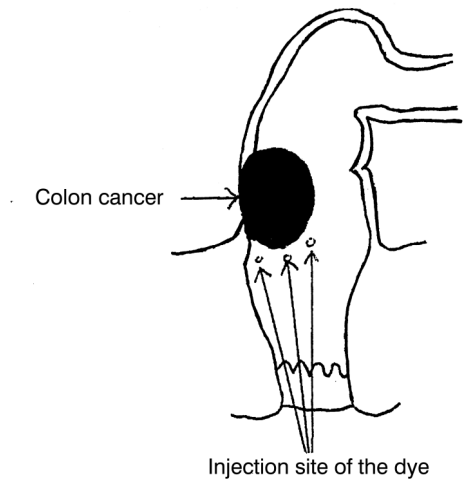

Figure 2. The technique of sentinel lymph node identification in patients with cancer of the rectum

In order to identify the SN we applied the dye technique described by Saha. In the case of cancers of the colon the dye (1% methylene blue) was applied as a subserous injections, in the case of cancer of the rectum – as a submucous injections, at four points; 0.5 ml at each injection (Figure 1). The staining of the lymphatic vessels and the lymph nodes was evaluated intra-operatively – in case of cancers of the colon 10-15 minutes after the application of the dye, while in case of cancers of the rectum – directly after the resection of the mesorectum (Figure 2).

During pathological examination the nodes were dissected every 100 μm and immunohistochemical (IHC) analysis was performed. IHC analysis was performed in 17 cases – in patients in whom the SN was found to contain no metastatic cells after routine HE staining.

Results

We identified the SN in 24 pts (95%) with cancer of the colon and in 10 pts (62%) with cancer of the rectum. In 3/41 pts the SN was the only lymph node containing metastases. In 19/41 pts no metastases were found in both the SN and in other regional lymph nodes (RLN). In 16/41 we found metastases in both the SN and RLN. In 3/41 pts only the RLN were found to contain metastases, whereas there was no SN involvement. In one case (5.8% of the entire group) IHC of the sentinel nodes revealed the presence of isolated cancer cells.

Another issue was the evaluation of the influence of disease advancement on the frequency of sentinel node identification. In our material of patients with cancer of the colon postoperative pTNM staging revealed 7 pts in stage I, (altogether 14 SN examined), 9 pts in stage II (altogether 11 SN examined) and 9 pts. in stage III (altogether 11 SN examined).

In case of patients with cancer of the rectum we found 12 pts in stage II (altogether 4 SN examined) and 4 pts. in stage III (altogether 2 nodes examined). There were no stage I patients in the rectal cancer group.

Discussion

The analysis of the SN in patients with colorectal cancer is still in the research stage [3]. Contrary to the treatment of melanoma and breast cancer in patients with colorectal cancer the identification of the sentinel lymph node does not affect the span of the lymphadenectomy, but it increases the frequency of identifying nodal metastases [4-13].

The first large report concerning the value of the SN in colorectal cancer, basing upon a study of 203 patients, had been published by Saha in 1999 [10]. He applied the staining technique, which allowed to identify the sentinel node in 98% of patients. Conventional pathological examination allowed to discern metastases in 36 patients (18%). A series of precise cuts of the SN allowed to identify micrometastases in yet another 16 cases, while IHC analysis increased this number by yet another 11 patients. This multicentered trial has shown that the identification of the sentinel lymph node and its

careful evaluation changed the staging from I and II to III acc. to AJCC in as many as 14% of patients. These 14% of patients could greatly benefit from adjuvant chemotherapy [14].

Bilchik et al. performed an analysis of the SN in 100 patients with colorectal cancer. Once again they used the staining method and identified the SN in 96% of cases. A series of cuts and IHC analysis increased the number of recognized metastases by 25 patients, i.e. stage of advancement increased in case of 40% of patients [15].

Similar promising results have been reported by Wood, who performed an analysis of 50 patients. The SN was identified in 94% of cases; detailed analysis of the SN verified the stage of advancement in 20% of cases, while in 6% of cases the results were falsely negative [16]. The same author applied the SN technique in the course of laparoscopic excision of the colon. SN staining was possible in the same percentage as in the case of classical laparotomy, while detailed examination allowed to discern micrometastases in 20% of patients [17-19].

According to Joosten et al. the concept of identifying the SN with the aid of dye has no prognostic value. He applied the technique in 35 cases and achieved false negative results in the SN, with the presence of metastases in other regional lymph nodes in 60% of cases [20].

In our material of 41 pts (25 with cancer of the colon and 16 with cancer of the rectum) the SN was identified in 24 pts with cancer of the colon (95%) and in 10 pts with cancer of the rectum (62%) [21]. In 17/41 pts in whom no metastases were found in both the SN and the RLN immunohistochemical methods have allowed to discern the presence of isolated cancer cells in 5.8% of patients, which allowed to change the staging from I and II to III.

The application of the SN technique is more complex in the case of cancer of the rectum. In the study reported by Bembenek et al. 48 patients had been evaluated with a sensitivity of 70%, although the SN had been identified in 96% of cases. In this study no significant changes of the stage of clinical advancement were observed [3].

Bilchik et al. have presented the results of the evaluation of the SN with the aid of cytokeratin and PCR. In his multicentered trial he evaluated the SN in 40 patients. In 53% of cases where, on classical examination, the nodes were found to contain no metastases he discerned micrometastases in the course of IHC analysis. Thus, it was possible to identify a subgroup of patients at greater risk of developing recurrence who could profit from adjuvant chemotherapy [22, 23].

Broll et al. have presented the results of an analysis of 49 pts with colorectal cancer. In patients initially pronounced as stage I and II IHC has allowed to discern micrometastases in as many as 26% of cases and in 33% of these patients recurrence was observed. Among the patients with no micrometastases recurrence was observed only in 12% of cases. This study also proves that the presence of micrometastases may, in fact, increase the risk of recurrence, but the relatively small number of enrolled patients does not allow for complete analysis and further studies on larger patient groups are necessary [24-28].

Our relatively small patient material does not allow to draw any binding conclusions which could throw light on this complex issue [21].

Tsavellas et al. have analyzed 9 publications concerning the role of the SN in colorectal cancer. In 8 of these reports identification was performed with the staining technique. Only in one study did the authors apply a combined dye-and-isotope technique. The number of patients in whom the evaluation of the SN altered the advancement stage of the disease is reported to be from 4 to 40%. The number of false negative results has increased from none to 40%. In case of patients in whom SN identification was performed with the aid of both dye and radioisotope the ratio of false negative results was 20% [29].

Prabhadesai stresses the necessity for performing further studies in order to evaluate the role of the SN in colorectal cancer before introducing it into clinical practice [30].

Yet another issue involved in the evaluation of the SN in colorectal cancer is the identification of the SN in the non-regional lymph nodes (the so-called "jumping metastases"). According to different authors their incidence varies from null to 7%, and in case of their identification the extent of nodal dissection should be increased [23].

Basing upon the analysis of literature reports one may conclude that the identification of the sentinel lymph node is relatively easy in patients with cancer of the colon, whereas in case of cancers of the rectum the matter becomes more difficult. Our study has provided similar results, as we have managed to identify the SN in 95% of patients with cancer of the colon and only in 62% of patients with cancer of the rectum[21].

The influence of the presence of micrometastases within the SN on patient prognosis is still the matter for many discussions. Broll et al believe that the presence of occult metastases discernible only immunohistochemically may influence the frequency of local recurrence and distant metastases and yet have no impact on the prognosis concerning overall survival [25]. On the other hand Nakanishi et al. believe that micrometastases have no effect of patient prognosis [31] while Liefers et al. have concluded that the presence of micrometastases influences the length of survival of patients with colorectal cancer [32].

Conclusions

The identification of the SN poses a problem in patients with cancer of the rectum and demands further study in order to evaluate the applicability of this method for the diagnostics of regional lymph node metastases

In patients with cancer of the colon the number of identified SN was higher in cases in a lesser stage of advancement

Attempts to evaluate the SN with immunohistochemical techniques allow to discern isolated cancer cells which could not be found with the aid of HE staining

There exists the necessity for long-term follow-up of patients with confirmed micrometastases to sentinel lymph nodes in order to evaluate the risk of their developing recurrence and to assess their survival.

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References

1. Didkowska J, Wojciechowska U, Tarkowski W et al. *Nowotwory złośliwe w Polsce w 2000 roku*. Warszawa: Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie 2003.
2. Nowacki M. Nowotwory jelita grubego. In: Wronkowski Z, Zwierko M. W: *Epidemiologia, czynniki ryzyka i możliwości zapobiegania*. Warszawa: Wydawnictwo Wiedza i Życie; 1996, 24-49.
3. Bembenek A, Bayrakter S, Gretschel S et al. Sentinel Lymphonodectomy in Gastrointestinal Cancer – Where are we now? *Onkologie* 2002; 25: 334-40.
4. Cabanas R. An approach for the treatment of penile carcinoma. *Cancer* 1977; 39: 456-66.
5. Morton DL, Wen DR, Wong JH.Technical details of inraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; 127: 392-9.
6. Krag D, Wear D, Ashikaga T. The sentinel node in breast cancer. *N Engl J Med* 1998; 339: 941-6.
7. Giuliano A, Kirgan D, Guenther J, Morton D. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; 220: 391-401.
8. Veronesi U, Galimberti V, Zurrida S et al. Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer. *Eur J Canc* 2001; 37: 454-8.
9. Morton D, Wen D, Cohran A. Management of erly-stage melanoma by intraoperative lymphatic mapping and selective lymphadenectomy: an alternative to routine elective lymphadenectomy or watch and wait. *Surg Oncol* 1993; 2: 335-9.
10. Saha S. Technical Details of Sentinel Lymph Node Mapping in Colorectal Cancer and Its Impact on Staging. *Ann Surg Onc* 1999; 7: 120-124.
11. Saha S, Bilchik A, Wiese D et al. Ultrastaging of Colorectal Cancer by Sentinel Lymph Node Mapping Technique – A Multicenter Trial. *Ann Surg Onc* 2001; 8: 94-8.
12. Arend E, Andre M, Lynne V. Diagnostic Use of the Sentinel Node in Colon Cancer. *Dis Colon Rectum* 2001; 44: 410-17.
13. Paramo J, Summerall J, Wilson C et al. Intraoperative sentinel lymph node in patients with colon cancer. *Am J Surg* 2001; 182: 40-43.
14. Wong J, Steineman S, Calderia C et al. Ex Vivo Sentinel Node Mapping in Carcinoma of the Colon and Rectum. *Ann Surg* 2001; 233: 515-21.
15. Bilchik J. Aberrant Drainage and Missed Micrometastases: The Value of Lymphatic Mapping and Focused Analysis of Sentinel Lymph Nodes in Gastrointestinal Neoplasms. *Ann Surg Onc* 2001;8:82-85.
16. Wood T, Tsioulias G, Morton D et al. Focused Examination of Sentinel Lymph Nodes Upstages Early Colorectal Carcinoma. *Am Surg* 2000; 66: 998-1003.
17. Kitagawa Y, Ohgami M, Fujii H et al. Laparoscopic Detection of Sentinel Lymph Nodes in Gastrointestinal Cancer: A Novel and Minimally Invasive Approach. *Ann Surg Onc* 2001; 8: 86-9.
18. Tsioulias G, Wood T, Spirt M. A Novel Lymphatic Mapping Technique to Improve Localization and Staging of Early Colon Cancer during Laparoscopic Colectomy. *Am Surg* 2002; 68: 561-5.
19. Tsioulias G, Wood T, Morton D et al. Lymphatic Mapping and Focused Analysis of Sentonel Lymph Nodes Upstage Gastrointestinal Neoplasms. *Aerch Surg* 2000; 135: 926-32.
20. Joosten J, Strobbe L, Wauters C et al. Intraoperative lymphatic mapping aand the sentinel node concept in colorectal carcinoma. *Brit J Surg* 1999; 86: 482-6.
21. Zieliński J, Jastrzębski T, Kopacz A et al. Biopsja węzła „wartownika" w raku okrężnicy i odbytnicy. Badanie pilotowe. *Ann Acad Med Gedan* 2003; 33: 271-6.
22. Bilchik A, Saha S, Wiese D et al. Molecular Staging of Early Colon Cancer on the Basis of Sentinel Node Analysis: A Multicenter Phase II Trial. *J Clin Onc* 2001; 19: 1128-36.
23. Bilchik J. Aberrant Drainage and Missed Micrometastases: The Value of Lymphatic Mapping nad Focused Analysis of Sentinel Lymph Node in Gastrintestinal Neoplasms. *Ann Surg Onc* 2001; 8: 82-5.
24. Kitagawa Y, Fujii H, Mukai M et al. The role of the sentinel lymph node in gastrointestinal cancer. *Surg Clin North Am* 2000; 80: 1799-1809.
25. Broll R, Schauer V, Schimmelpenning H et al. Prognostic Relevance of Occult Tumor Cells in Lymph Nodes of Colorectal Carcinomas. *Dis Colon Rectum* 1997; 40: 1465-71.
26. Wittekind C. Pathologische Aspekte der Sentinel – Lymphknoten – Biopsie. *Der Onkologie* 2003; 6: 650-4.
27. Wiese D, Saha S, Badin J. Pathologic Evaluation of Sentinel Lymph Nodes in Colorectal Carcinoma. *Arch Pathol Lab Med* 2000; 124: 1759-63.
28. Waters G, Geisinger K, Garskie D. Sentinel Lymph Node Mapping for Carcinoma of the Colon: A Pilot Study. *Am Surg* 2000; 68: 943-945.
29. Tsavellas G, Huang A, Allen-Mersh G. Does sentinel lymph node biopsy have a role in colorectal cancer? *Colorectal Dis* 2002; 4: 158-61.
30. Prabhudesai A, Kumar D. The sentinel lymph node in colorectal cancer-of clinical value? *Colorectal Dis* 2002; 4: 162-6.
31. Nakanishi Y, Ochiai A, Yamauchi Y et al. Clinical Implications of Lymp Node Micrometastases in Patients with Colorectal Cancers. *Oncology* 1999; 57: 276-80.
32. Liefers G, Cleton-Jansen A, Van De Velde C et al. Micrometastases and survival in stage II colorectal cancer. *New Engl J Medin* 1998; 339: 223-8.

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