

Circulating and disseminated tumor cells: oncologists' little helpers?

Wojciech M. Wysocki

1 Department of General, Oncological and Vascular Surgery, 5th Military Hospital in Kraków, Kraków, Poland

2 Department of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Kraków, Poland

3 Scientific Editorial Office, The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

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by Pach et al,
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With many tailored, patient-oriented molecular therapies developed in recent years, modern oncology has become more and more individualized. Classic clinical entities we all were taught in medical schools are no longer valid as a base for therapeutic decisions. Colorectal cancer is an excellent example of the ongoing subclassification of the disease into smaller, narrower entities. Apart from the obvious anatomical distinction between right- and left-sided colon tumors, relevant biological and molecular differences are well known nowadays, which has a significant impact on therapeutic decisions (TABLE 1).¹

Complex, multidisciplinary, and long-term oncological treatment requires novel prognostic and predictive factors. These factors are needed to support clinical decisions by assessing prognosis in specific subgroups of patients and/or predicting their potential susceptibility to specific high-end molecular therapies. Among many others, the prognostic and/or predictive value of circulating tumor cells (CTC) has been postulated and proven,^{2,3} also in patients with colorectal cancer.^{4,5} Disseminated tumor cells (DTCs), studied by Pach et al,⁶ are a fraction of CTCs, which are capable of entering distant organs (like the bone marrow) and persisting there.²

Data on the prognostic value of CTCs are abundant,^{4,5} but evidence regarding the particular role of DTCs in colorectal cancer is not consistent. Disseminated colorectal cancer cells are present in peripheral blood in almost a half of patients with colorectal cancer with hepatic metastases, and in a quarter of this population, they can be found in the bone marrow too.^{6,7} Presence of DTCs in the bone marrow was shown to be an independent negative prognostic factor for overall survival in these patients. This observation supports the concept that DTCs present in the bone marrow indicate an increased tumor burden and, therefore, might serve as an additional individual marker for proper selection of patients for adjuvant

treatment after curative surgery.⁷ Disseminated tumor cells in the bone marrow can be a reservoir of cancer cells and may—after a period of dormancy—re-enter the vasculature and secondarily disseminate throughout the body.⁸

With no doubt, the study by Pach et al,⁶ which appeared in the current issue of *Polish Archives of Internal Medicine (Pol Arch Intern Med)*, refers to nowadays valid issues related to DTCs. Results presented by the authors are, however, somewhat unexpected: in left-sided colon and rectal cancers, the presence of DTCs in the bone marrow seemed to diminish the risk of metastasis formation. There was also a trend toward improved survival in DTC-positive patients. This is contrary to the “gut feeling” supported in other studies,⁷ which suggested that dissemination of cancer cells in the bone marrow is a negative rather than positive prognostic factor.

Furthermore, I found it interesting that the presence of DTCs in the bone marrow was not correlated with the depth of tumor infiltration into the bowel wall and there was no increase in the risk of bone marrow positivity for DTCs in node-positive patients compared with those node-negative. The presence of DTCs was not related to the tumor grade as well. This means that there was no correlation among DTCs in the bone marrow and the most potent prognostic factors defined in the classic TNM system, ie, tumor size, lymph node metastases, and dedifferentiation of colorectal cancer. As a consequence of lack of correlation among DTCs and major classic prognostic factors (tumor size [T], node involvement [N], and histopathological grade), I found it not surprising that the authors were actually not able to attribute any clear prognostic value to the presence of DTCs in terms of 5-year survival (even after excluding early stage, stage I, and advanced, stage IV, patients).

There are 2 major strengths of the study by Pach et al⁶: 1) an attempt to include a homogenous

Correspondence to:

Prof. Wojciech M. Wysocki, MD, PhD,
Department of Surgery, Faculty
of Medicine and Health Sciences,
Andrzej Frycz Modrzewski Krakow
University, ul. Gustawa Herlinga-
Grudzińskiego 1, 30-705 Kraków,
Poland, email: wwyssocki@mp.pl

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TABLE 1 Selected features of right- and left-sided colon cancers (based on Baran et al¹)

Feature	Right-sided colon cancer	Left-sided colon cancer
Incidence	Increasing	Decreasing
Predominantly affected sex	Female	Male
Clinical presentation	Late onset, mainly anemia	Early onset, stenosis, and change in bowel movements
Mucinous type	Frequent	Infrequent
Genetics	Common site for <i>MUTYH</i> -associated polyps, sessile serrated polyps	Common site for <i>AFP</i> -related polyps, tubular or villous adenocarcinoma
Immunology	More active immune cells promoting immunogenicity, high T-cell tumor infiltration	Less active immune cells promoting tolerance, low T-cell tumor infiltration
Predominant	Mutations in the DNA mismatch, repair pathways, <i>MSI</i> / <i>BRAF</i> -positive tumors	Chromosomal instability–positive tumors; <i>KRAS</i> , <i>APC</i> , <i>PIK3CA</i> , and <i>p53</i> gene mutations
Treatment inducing a better response	Immunotherapy	Cytotoxic chemotherapy and targeted therapies
Prognosis	Generally better	Generally worse

study group (only left-sided colon and rectal tumors) and 2) long-term follow-up (all patients were followed up for at least 5 years or until death, whichever occurred first). The results of the study are generally in line with those presented in the medical literature. However, as the authors correctly stated in the discussion, the results reported by others are often conflicting (see the discussion section by Pach et al⁶).

My own conclusion drawn from that study is that DTCs, a fraction of CTCs, which are currently extensively studied in various primary malignancy types as an additional, potentially valuable prognostic factor, still do not play a role in routine clinical practice. I would speculate that not just the presence or absence of DTCs in a specific organ like the bone marrow would help in clinical decision-making, but maybe the size of DTC clusters in the bone marrow or their mitotic activity would play that role. Therefore, I am waiting for studies to come in the next years.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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