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Peritumoral deposits as an adverse prognostic indicator of colorectal cancer

Hideki Ueno, M.D., Ph.D.[a,*], Yojiro Hashiguchi, M.D., Ph.D.[b], Hideyuki Shimazaki, M.D., Ph.D.[c], Eiji Shinto, M.D., Ph.D.[a], Yoshiki Kajiwara, M.D., Ph.D.[a], Kuniaki Nakanishi, M.D., Ph.D.[c], Kei Kato, M.D., Ph.D.[c], Kazuya Maekawa, M.D.[c], Takahiro Nakamura, Ph.D.[d,e], Junji Yamamoto, M.D., Ph.D.[a], Kazuo Hase, M.D., Ph.D.[a]

[a]Department of Surgery, National Defense Medical College, 3-2, Namiki, Tokorozawa, Saitama 359-8513, Japan; [b]Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan; [c]Department of Laboratory Medicine, National Defense Medical College, Tokorozawa, Japan; [d]Laboratory for Mathematics, National Defense Medical College, Tokorozawa, Japan; [e]Laboratory for Statistical Analysis, Center for Genomic Medicine, RIKEN, Yokohama, Japan

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Prognosis

Abstract

BACKGROUND: The aim of this study was to determine the prognostic value of peritumoral deposits (PTDs) in colorectal cancer (CRC).

METHODS: A total of 695 patients with pT3/T4 CRC (1980 to 1999) were reviewed. Tumor deposits located ≥2 mm from the front of the direct spread in the primary tumor were evaluated as PTDs.

RESULTS: PTDs were observed in 111 patients (16.0%). The incidence of PTDs increased according to increasing N stage: 7% for N0, 22% for N1, and 39% for N2 ($P < .0001$). Five-year disease-specific survival was 85.0% in patients without PTDs and 59.5% in those with PTDs ($P < .0001$). Multivariate analysis showed that PTDs affected disease-specific survival independent of T and N stages. A significant prognostic impact of PTDs was similarly observed in another cohort comprising 474 patients with pT3/T4 CRC (2000 to 2005). The κ values among 8 observers were .70 for PTDs and .32 for the conventional growth pattern.

CONCLUSIONS: PTDs have considerable prognostic relevance and offer improved judgment reproducibility in assessing the invasive margin of CRC.

Discontinuous cancer spread is well recognized as a distinctive growth pattern associated with surgical resection margin involvement and postoperative local failure in rectal cancer,[1–6] but there have been few attempts to determine the histologic boundary between continuous and discontinuous cancer spread. In the 7th edition of the American Joint Committee on Cancer staging manual,[7] it is recommended that tumor deposits be considered as a prognostic factor. However, there is no definition of discontinuous spread length, which is important because this is what leads to cancer lesions' being regarded as tumor deposits of prognostic importance.

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* Corresponding author. Tel.: +1-81-42-995-1637; fax: +1-81-42-996-5205.

E-mail address: ueno@ndmc.ac.jp

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The nature of the invasive margin is believed to be closely linked to the biologic behavior of tumors, and an invasive growth pattern is a well-known prognostic indicator in colorectal cancer (CRC).[8–12] For example, a 2-grade system of invasive growth pattern (expanding or infiltrating) was used in Jass et al's[13] grading system. In Japan, pathologic reports use a 3-grade system for identifying invasive patterns (expanding, intermediate, or infiltrating).[14] However, invasive growth patterns have conventionally been assessed subjectively, and results from interobserver studies have shown considerable inconsistency in judgment.[15,16] Thus, new histologic criteria to improve the objectivity of this judgment are required for assessing the nature of invasive patterns.

In this study, we attempted to determine whether obtaining reasonable histologic criteria for defining extramural discontinuous spread of CRC was possible and attempted to clarify the clinical significance of the classification of the nature of the invasive margin on the basis of the degree of discontinuous spread.

Methods

Patients

We reviewed a total of 695 patients with pathologically confirmed T3 or T4 advanced colorectal adenocarcinoma treated with surgery with curative intent in the Department of Surgery, National Defense Medical College (Tokorozawa, Japan), from 1980 to 1999 (cohort 1). There were 401 men and 294 women with an average age of 62.0 years at the time of surgery (range, 21 to 87 years). We identified colon cancers in 465 patients and rectal cancers in 230 patients. All patients were followed for $\geq$5 years or until death, and the mean follow-up period among survivors was 8.7 years. No patients received preoperative or postoperative therapies such as radiation therapy or intensive chemotherapy with intravenous administration of chemotherapeutic agents, although some patients received postoperative oral administration of anticancer agents such as 5-fluorouracil, tegafur-uracil, 5′-doxifluridine, or 1-hexylcarbamoyl-5-fluorouracil.

To validate our results, a 2nd cohort of 474 patients (268 men, 206 women; average age, 65.6 years; range, 18 to 96 years) with T3 or T4 CRC who consecutively underwent curative surgery at the same institution from 2000 to 2005 were enrolled. Of these, 382 patients had colon cancer, and 92 had rectal cancer. None received any preoperative therapy. Regarding postoperative adjuvant chemotherapy, 228 patients received chemotherapy, 88 received 5-fluorouracil plus leucovorin, 53 received tegafur-uracil plus leucovorin, and 87 received oral anticancer drugs such as tegafur-uracil, 5′-doxifluridine, 1-hexylcarbamoyl-5-fluorouracil, or 5-fluorouracil. No adjuvant therapy was administered to 238 patients, and no detailed information regarding postoperative adjuvant therapy could be obtained for 8 patients. Detailed prognostic information, including the recurrence pattern 5 years after surgery, was obtained for 457 patients (96.4%), and the median follow-up period among the 355 survivors was 68 months.

Histologic evaluation

Surgically resected specimens were routinely processed according to the guidelines of the Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus.[14] Surgeons harvested the mesenteric lymph nodes from fresh surgical specimens. Peritumoral fatty tissue was treated in a no-touch manner during this process to accurately conduct a histopathologic evaluation of the status of the circumferential surgical margin.

After fixation in formalin solution, the primary tumors were sectioned along the long axis of the intestine. Several tissue blocks, including those from the section crossing the deepest part of the tumor and those thought to require inspection by a pathologist, were used as pathologic specimens. Histologic evaluation used all hematoxylin and eosin–stained glass slides of the primary tumor lesion made as part of routine practice; the median number of glass slides per patient was 5 (range, 1 to 19) in cohort 1, and all of these were used for evaluating the status of discontinuous spread of the cancer. In cohort 2, we evaluated the status of discontinuous spread using only glass slides prepared from a single longitudinal section of the whole tumor, including its deepest part. The median number of glass slides examined was 2 (range, 1 to 10) per patient in this cohort. Pathologic examination confirmed that no tumors had circumferential surgical involvement in both cohorts 1 and 2.

Assessment of the distance of discontinuous spread (Fig. 1)

The shortest distance of the cancer deposit from the extramural lesion of the primary tumor (the distance of discontinuous spread) was measured on the glass slides (original method); cancer deposits with discontinuous spread $\geq$ 2 mm were recorded as peritumoral deposits (PTDs). For measurement of the distance of discontinuous spread for tumor deposits that did not have the extramural lesion of the primary tumor to be regarded as an appropriate standard of measurement (ie, when a tumor deposit was observed on glass slides not containing part of the main lesion or when a deposit was located closer to the muscularis propria than the advancing edge of the primary tumor), the vertical length from the deepest border of the muscularis propria was measured (alternative method).

PTDs were classified as nodular type (a tumor nodule without residual lymph node structure), or non-nodular type (isolated foci of vascular/perineural invasion),[17,18] and the maximum diameter of each tumor deposit was measured.