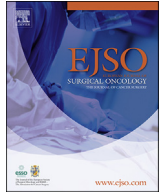




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Proposal of a stage-specific surveillance strategy for colorectal cancer patients: A retrospective analysis of Japanese large cohort

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ABSTRACT

Background: Frequency and duration of postoperative surveillance for colorectal cancer patients remain debatable, and follow-up data regarding stage I or resected stage IV patients are limited.

Method: Cohort data from 22 institutions were retrospectively analyzed; 18,841 patients who underwent curative surgery for stage I to IV cancer were included. The cumulative incidence of recurrence, recurrence rate over surveillance period, and risk of recurrence each year after surgery were assessed.

Results: Recurrence rates in stages I, II, III, and IV were 4.2%, 14%, 32%, and 75%, respectively. Over 80% of recurrences occurred within the first 2 years in stage IV, and 3 years in stages II and III, whereas 86.8% of recurrences occurred in 5 years in stage I. Among patients with 5-year recurrence-free survival, 2.2% in stage III and 7.0% in stage IV still experienced recurrence after the 5-year postoperative period. When the duration is extended to 6 years in stage III and 8 years in stage IV, approximately 1% over the surveillance period would be achieved. In stage I, the risk of recurrence each year after surgery was consistently low, whereas the risks in stages II, III, and IV were high in the early postoperative phase. The risk of recurrence each year in stages III and IV patients were over 2-fold and 6-fold higher than that in stage II, respectively. **Conclusions:** Recurrence patterns were markedly different according to cancer stages. These results suggest that a stage-specific approach to postoperative surveillance may improve the efficiency of detecting recurrences.

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Introduction

In the 1990s, many randomized controlled trials (RCTs) compared the outcomes of high-intensity postoperative surveillance for detecting recurrence in colorectal cancer patients with those of low-intensity surveillance, and since the 2000s, several meta-analyses have indicated that high-intensity surveillance can improve the detection rate of recurrence, surgical resectability for recurrence, and survival after surgery [1–5]. Since then, major Western organizations, such as the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO),

started to recommend high-intensity surveillance strategies in their treatment guidelines. Meanwhile, in Japan, high-intensity surveillance has been conventionally performed equally even for stage I or resected stage IV patients [6]. Both the Western and the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines recommend 5 years of surveillance, with short examination interval during the first 2 or 3 years (Supplemental Table 1) [7–11]. The ASCO and JSCCR guidelines state that in stages II and III patients, 80% of recurrences occur during the first 3 years, and 95% occur within 5 years [7,11]. The JSCCR guidelines also states that recurrence over 5 years after surgery only occurs in less than 1% of stage I to III patients; similarly, the Adjuvant Colon Cancer End-points (ACCENT) Group reported that recurrence rate after 5 years was less than 1.5% per year in stage II or III colon cancer patients [11,12].

The incidence pattern of recurrence is different among cancer stages, and a uniform strategy across stages for detecting

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recurrences is inefficient. However, stage-specific surveillance is less likely to be used in these current guidelines. In addition, consensus on surveillance for stage I or resected stage IV patients has not been obtained because the previous RCTs include only few stage I patients or no resected stage IV patients. An optimal surveillance schedule has not been established, and its development is an important issue for cost and burden on both patient and medical provider. In this study, we planned to evaluate stage-specific recurrence pattern and to propose a more reasonable surveillance strategy in terms of visit interval, surveillance duration, and frequency of examination in each stage by analyzing multi-institutional cohort data of more than 18,000 patients.

Methods

Data source and study population

This is a retrospective study using multi-institutional cohort data. This cohort project was conducted by the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer in collaboration with 22 leading hospitals for cancer care across Japan, 15 university hospitals and 7 medical centers, and was approved by the Central Institutional Review Board (Tokyo Medical and Dental University). The study protocol was approved by the local ethical committee. Patients who underwent curative surgery for pathological stages I to IV (American Joint Committee on Cancer and Union for International Cancer Control) primary colorectal cancer between January 1997 and December 2006 were eligible. In terms of stage IV, only the patients who underwent both resection of primary colorectal cancer and radical metastasectomy for synchronous metastasis with R0 resection were included. The rate of missing data on the status of recurrence was low (2.7%), and complete case results were adopted as the main analyses. Data regarding patient characteristics, clinical and pathological tumor findings, adjuvant treatment, recurrence, first treatment for recurrence, and survival after surgery were collected.

Statistical analysis and definition

Recurrence patterns were primarily assessed: cumulative incidence of recurrence was evaluated by plotting Kaplan-Meier curves; recurrence rate over 5 years after surgery was calculated among both the whole study population and the patients with 5-year recurrence-free survival. We also estimated the risk of recurrence among patients who underwent postoperative surveillance in each year after surgery. The number of patients who underwent postoperative surveillance varied over time; therefore, it was replaced by the number of patients with recurrence-free survival until the beginning of the year, which was analyzed by using the Kaplan-Meier curve. This study addressed only first recurrences following curative resection. Recurrence-free survival time was measured from date of surgery to first recurrence or last follow-up, whereas in stage IV with curative resection, it was defined as disease-free survival time measured from when primary tumor resection and metastasectomy for synchronous metastasis were both completed. Resectable recurrence was defined as recurrence that was surgically resected, and recurrence treated with chemotherapy alone, ablation, or best supportive care was defined as unresected. We used the Cox proportional hazard model to estimate hazard ratios with 95% confidence interval (CI) for overall survival after recurrence. All statistical analyses were performed using the software *JMP Pro* version 11 (SAS institute, Cary, North Carolina, US).

Results

Characteristics of cohort patients

Our study cohort included 19,749 consecutive patients who underwent curative surgery for stages I to IV colorectal cancer between 1997 and 2006; of these, 336 were ineligible because of the following factors: stage 0 or unknown ($n = 115$); appendix or proctodeum cancer ($n = 195$); and unknown tumor location ($n = 26$). Cases in which tumor was not an adenocarcinoma (e.g., adenosquamous carcinoma or squamous cell carcinoma) ($n = 52$) and those with missing data on the status of recurrence ($n = 520$) were excluded from this study. Finally, a total of 18,841 patients were included: 4838 patients with stage I disease; stage II, 6152; stage III, 6843; and stage IV, 1008.

Recurrence pattern

In the entire follow-up duration of this study, recurrence rate was 4.2%, 14%, 32%, and 75% in stages I, II, III, and IV, respectively (Table 1). In this cohort, median follow-up durations among patients with recurrence-free survival were at least 6.7 years in every stage. The number of resected stage IV patients with synchronous metastatic sites was as follows: 645 patients (64%) had liver metastasis; 78 (8%), lung; 24 (2%), liver and lung; 149 (15%), peritoneum; and 112 (11%), other organs (Table 2). The recurrence in resected stage IV patients was common in organs that were previously operated on.

Fig. 1 shows the time to incidence of recurrence in each stage. In stages II to IV, the recurrence was more likely to occur in the early phase of the surveillance period, whereas in stage I, the incidence curve was more linear. A steep curve was observed in stage IV. A total of 82.9% and 86.5% of recurrences developed within 3 years after surgery in stages II and III, respectively, and 86.1% developed within only 2 years in stage IV. Meanwhile, in stage I, only 66.7% of recurrences occurred in the first 3 years, and 86.8% occurred in 5 years.

The data regarding recurrences occurring over 5 years after surgery are shown in Table 3. The incidence rate of recurrence in each stage was approximately 1% (0.5–1.3%) among all patients who underwent surgery and were candidates for postoperative surveillance. However, 2.2% of patients in stage III and 7.0% in stage IV still experienced further recurrence among the patients who could have a 5-year recurrence-free survival. In stage III, 1.1% (31/2755) of patients with supposed recurrence-free survival for 6 years after surgery developed recurrence. Similarly, in stage IV, recurrences occurred in 4.6% (7/153), 3.3% (4/120), and 1.2% (1/81) of patients with recurrence-free survival of 6, 7, and 8 years, respectively. Hence, approximately 1% of recurrence rate over the surveillance period would be observed if the duration is 6 years in stage III and 8 years in stage IV.

In terms of risk of recurrence each year after surgery, the number of patients with recurrence-free survival at the beginning of the year was used as the number of population at risk, who were assumed to undergo postoperative surveillance each year. The risk of recurrence each year after surgery in each stage is shown in Fig. 2A. The risk in stage I was consistently low (less than 1.1%) throughout the 5-year postoperative period, whereas that in stages II, III, and IV was likely high in the early postoperative phase. The risk each year in stage II was 2.8–4.6% in the first 3 years and that in stages III and IV was over 2-fold (5.9–13.1%) and 6-fold (19.4–45.3%) higher than that in stage II, respectively. During the overall follow-up period, surgical resectability following detection of recurrence was approximately 40% in each cancer stage: 48.0% (97/202) in stage I; 44.7% (373/835) in stage II; 38.1% (823/2161) in

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