ANTICANCER RESEARCH *35*: 4903-4908 (2015)

Stereotactic Body Radiotherapy Results for Pulmonary Oligometastases: A Two-Institution Collaborative Investigation

YUZURU NIIBE[1,3], HIDEOMI YAMASHITA[2], KENJI SEKIGUCHI[3], WATARU TAKAHASHI[2], KENSHIRO SHIRAISHI[2], KAE OKUMA[2], ATSURO TERAHARA[2,3], JIRO KAWAMORI[3] and KEIICHI NAKAGAWA[2]

[1]*Department of Radiology, Toho University Omori Medical Center, Ota-ku, Tokyo, Japan;*
[2]*Department of Radiology, the University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan;*
[3]*Department of Radiation Oncology, St. Luke's International Hospital, Chuo-ku, Tokyo, Japan*

Abstract. *Aim: The current study investigated outcomes and prognostic factors of pulmonary oligometastases at two Institutions. Patients and Methods: SBRT (stereotactic body radiotherapy) as performed for pulmonary oligometastases from January 2004 to April 2014, and patients with a biologically effective dose (BED_{10}) ≥75 Gy were registered in the study. Control of the primary tumor was not a criterion: we included both oligo-recurrence and sync-oligometastases. Results: A total of 34 patients were enrolled in the study. The median overall survival was 20 months (range=1-119 months) and the 2-year overall survival rate was 65.7% [95% confidence interval (CI)=48.3-83.1%]. The two-year local control rate was 79.1% (95% CI=62.4-95.8%). Stratified by oligo status, the 2-year overall survival rate of the oligo-recurrence group was 68.5% (95% CI=50.3-86.7%), while that of the group with sync-oligometastases was 50.0% (95% CI=1.0-99.0%). These rates were significantly different (p=0.037). No grade 5 early- or late- adverse events were recognized in the current study. Conclusion: SBRT for pulmonary oligometastases achieved good results and there was no serious adverse event. The oligo-recurrence group, in particular, achieved fairly good results.*

For a long time, patients with recurrence or metastasis of cancer have been considered to be in a terminal stage. Patients with distant recurrence or metastases receive systemic therapies strictly aimed at prolonging survival or relieving symptoms as palliation.

Hellman and Weichselbaum proposed the concept of 'oligometastases' in 1995 (1). In this concept, the primary tumor was active, with a few distant metastases, but 'oligometastases' implied that patients could live longer with local treatment (surgery, radiotherapy, radiofrequency ablation) of the distant recurrences/metastatic sites. At about the same time, Niibe performed radiotherapy for an abdominal para-aortic node in a case of isolated recurrence of cervical cancer at the National Institute of Radiological Sciences hospital in Japan, and achieved long-term survival, ultimately reporting in 2003 that c-ERBB2/HER2 (human epidermal growth factor receptor 2) is a prognostic factor for radiotherapy for such patients, and that such treatment can achieve a 5-year survival rate of 38% (2). Thereafter, multi-institutional retrospective studies on radiotherapy of isolated para-aortic nodes in uterine cervical cancer were undertaken, with similar results (3, 4). Moreover, investigations of patients with controlled primary lesions and brain metastases treated by stereotactic radiosurgery were performed and also led to good results (5). In 2006, Niibe *et al.* proposed a new concept that refined the concept of oligometastases to 'oligo-recurrence' (3-10), a state in which the primary tumor is controlled and only around 1-5 distant recurrences or metastases appear, for which local treatment of the distant recurrences/metastases can result in longer survival with better quality of life.

Niibe and Chang proposed the concept of sync-oligometastases (7). This is similar to the notion of oligometastases first suggested by Hellman and Weichselbaum with 1-5 distant recurrences/metastases and an active primary tumor; they argued that such patients benefit from local treatment to both the distant lesions and the primary tumor. Thus, the state for performing local treatment both for 1-5 distant recurrent/metastatic lesions and the primary tumor has been defined as 'sync-oligometastases'.

Correspondence to: Associate Professor Yuzuru Niibe, MD, Ph.D., Department of Radiology, Toho University Omori Medical Center, 6-11-1, Omorinishi, Ota-ku, Tokyo 143-8541, Japan. Tel: +81 337624151, Fax: +81 337685386, e-mail: yniibe-toho@umin.org

Key Words: Pulmonary oligometastases, SBRT, oligo-recurrence, sync-oligometastases.

Figure 1 depicts the states of oligo-recurrence and sync-oligometastases. The primary tumor is controlled in the case of oligo-recurrence with only a few distant recurrences/metastases. In sync-oligometastases, both the primary tumor and distant recurrences/metastases are active.

The current study investigated SBRT (stereotactic body radiotherapy) for pulmonary oligometastases and treatment outcomes. At the same time, we examined the prognostic difference between oligo-recurrence and sync-oligometastases and examined other prognostic factors previously reported.

Patients and Methods

SBRT for pulmonary oligometastases was performed at the St. Luke's International Hospital or the University of Tokyo Hospital, from January 2004 to April 2014, and patients registered were those treated with BED_{10} ≥75 Gy (the current study adopted α/β=10). The study was approved by the Ethics Committees of both institutions.

Control of the primary tumor was not a criterion: we included both oligo-recurrence and sync-oligometastases cases in the study.

A radiotherapy dose of 12-12.5 Gy, by four fractions, to a total SBRT dose of 48-50 Gy was given to 20 out of 34 patients. This was the main treatment method in the study. The other 14 patients were treated by SBRT using 5 to 8 Gy/fraction and a total of 7 to 10 fractions because the target tumor was situated in the medial side.

Survival curves and local control curves were constructed by the Kaplan–Meier method; a curve was drawn for every potential prognostic factor, and significant differences were determined by the log-rank test. The level of significance was set at the 0.05 alpha level. All statistical analysis was performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA).

Table I. *Patient's characteristics.*

Variable		Value/No. of patients
Gender	Male	22
	Female	2
Age (years)	Median	69.5
	Range	25-88
Karnofsky Performance Status	Median	90
	100	2
	90	20
	80	7
	70	3
	60	1
	50	1
Oligostatus	Oligo-recurrence	30
	Sync-oligometastases	4
No. of metastatic tumors	1	29
	2	5
	>3	0
Maximum tumor diameter (mm)	Median	16
	Range	8-40
Tumor origin	Lung	11
	Esophagus	6
	Colon + rectum	5
	Uterus	5
	Head + neck	2
	Other	5
Follow-up (months)	Median	20
	Range	1-119
Disease-free interval (months)	Median	29
	Range	0-116

Results

Patients. Thirty-four patients on whom SBRT of BED_{10} ≥75 Gy was performed from January 2004 to April 2014 were enrolled in the current study. Patient's characteristics are listed in Table I. The patients included 22 men and 12 women, with a median age of 69.5 years (range=25-88 years). Most patients (32/34) had a Karnofsky Performance Status of 70 or more. Regarding the oligostatus, 30 patients were included in the oligo-recurrence group, and four patients in the sync-oligometastases group. In the oligo-recurrence group, the disease-free-interval (DFI), which was the time to recurrence from the start of primary treatment until the date of onset of distant recurrence/metastasis, was a median of 29 months (range=0-116 months). Of course, in the sync-oligometastases group, the DFI was 0 months.

Survival and local control. The median overall survival of the whole patient cohort was 20 months (range=1-119 months) and the 2-year overall survival rate was 65.7% [95% confidence interval (CI)=48.3-83.1%]. These results were fairly good (Figure 2). The 2-year local control rate was also good at 79.1% (95% CI=62.4-95.8%) (Figure 3).

When stratified by oligostatus, the 2-year overall survival rate of the oligo-recurrence group was 68.5% (95% CI=50.3-86.7%), while the 2-year overall survival of the sync-oligometastases group was 50.0% (95% CI=1.0-99.0%). These rates were statistically different (p=0.037) (Figure 4). Stratified by histopathology, in order to compare the typically reported poor results of colon and rectal cancer with those of other primary cancer types, the 2-year overall survival rate for patients with colon and rectal cancer was 66.7% (95% CI=13.4-100%) while the 2-year overall survival rate of patients with other types was 66.2% (95% CI=48.0-84.4%). There was no statistically significant difference in outcome by primary site (p=0.878) (Figure 5). Regarding the local control rate, the 2-year local control rate in patients with cancer of the colon and rectum was 100% while that of patients with other types was 77.6% (95% CI=60.0%-95.2%; p=0.507) (Figure 6). Stratified by DFI, the 2-year overall survival of patients with a DFI ≥24 months was 81.9% (95% CI=63.3%-100%), while that of those with a DFI <24 months was 41.8% (95% CI=12.8-70.8%). These results achieved statistical significance (p<0.001) (Figure 7).

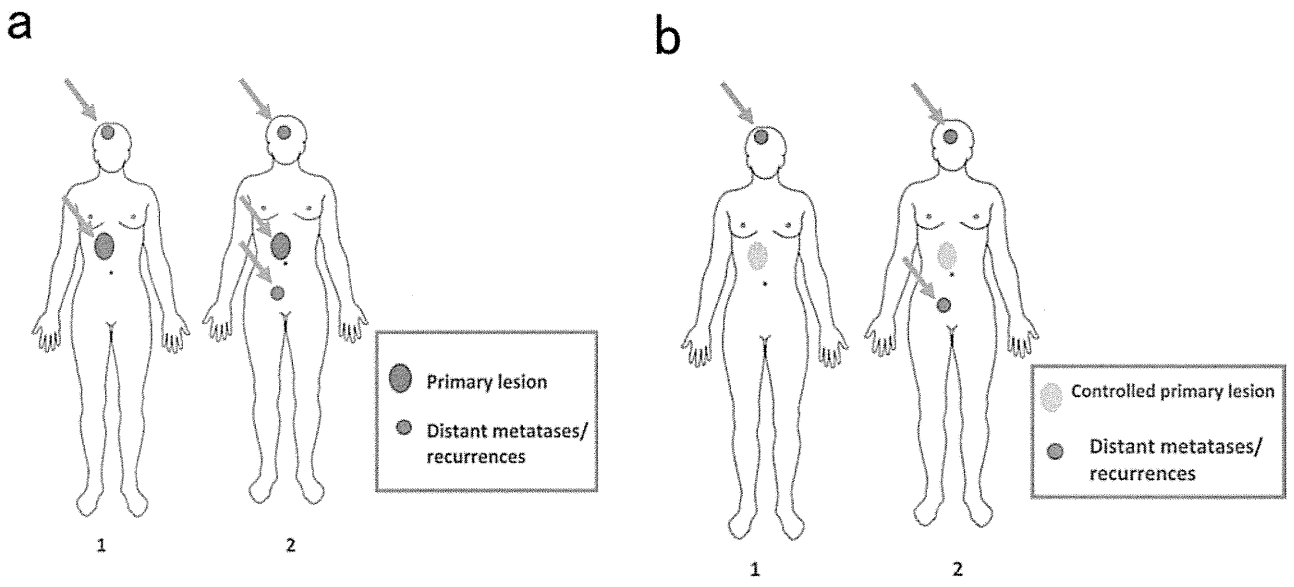

Figure 1. *Schema of sync-oligometastasis and oligo-recurrence. a: In sync-oligometastasis, there are several distant recurrent or metastatic lesions and an active primary lesion. Both distant and recurrent or metastatic lesions should be treated and any active primary lesion by local treatment, if possible. b: Schema of oligo-recurrence. There are several distant recurrent or metastatic lesions and a controlled primary lesion. Only distant recurrent or metastatic lesions should be treated locally. Partially modified from Niibe et al. (6).*

Adverse events. Regarding adverse events, one grade 4 event occurred in the acute phase. The case was a 59-year-old man with esophageal cancer, whose esophagus had been rebuilt with a gastric tube. Perforation occurred in the gastric tube. However, this event was thought to be due to the patient's general debility rather than being a side-effect of SBRT (using 48 Gy/4 fractions and no hot spot in the gastric tube area), since the patient was a heavy smoker and an alcoholic, and his overall status was weakened by these habits.

No late adverse events of grade 3 or more occurred according to the criteria of Radiation Therapy Oncology Group-The European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scheme (11).

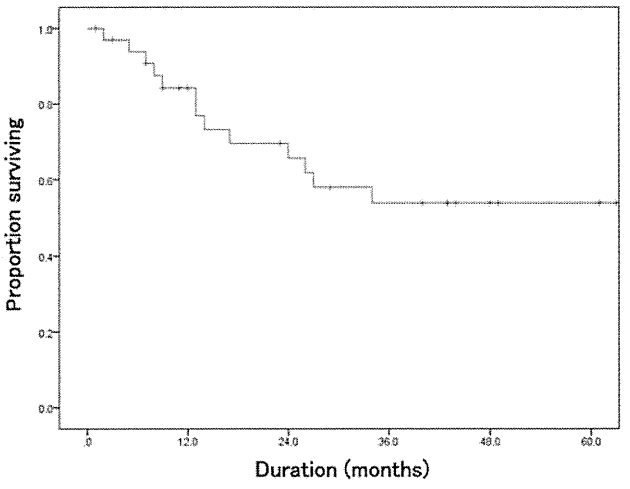

Figure 2. *Overall survival of patients. The median survival time was 20 months (range=1-119 months). The 2-year overall survival rate was 65.7% (95% confidence interval=48.3%-83.1%).*

Discussion

It has been 20 years since the concept of oligometastases was proposed in 1995, but it is only in the recent past that the concept has begun to attract attention. The International Registry of Lung Metastases (IRLM) reported that the 5-year survival rate of completely resectable pulmonary metastasis cases was 36% when patients were operated on (12). However, as imaging and biochemical tests had not progressed very far at that time, it was difficult to predict the likelihood of complete resection before surgery. Furthermore, there were often numerous metastases even when physicians could find only one metastasis. Recently, rapid progress in such technologies as computed tomography, magnetic resonance imaging, and positron emission tomography-computed tomography and their integration make it easier to detect a state of oligometastases, including patients with isolated pulmonary metastasis. Tumor markers are also often measured regularly and are thought to contribute to the finding of several pulmonary metastases. One more reason

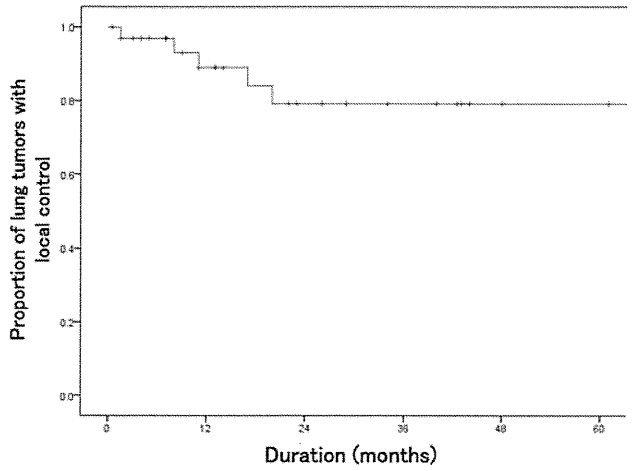

Figure 3. *Local control rate for the whole patient group. The 2-year local control rate was 79.1% (95% confidence interval=62.4-95.8%).*

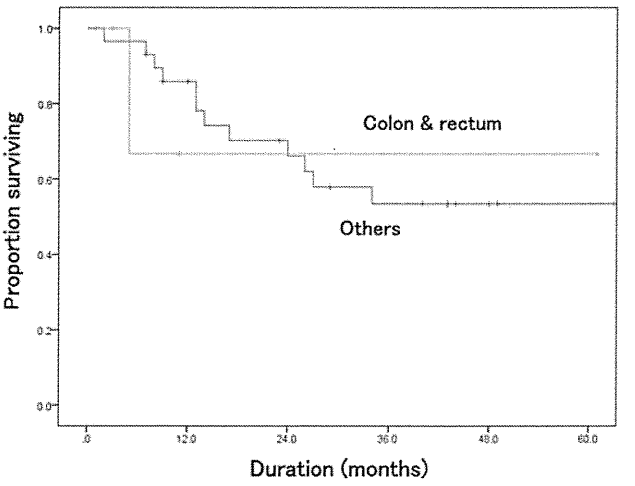

Figure 5. *Overall survival stratified by histopathology. Comparing patients with colon and rectal cancer to those with other cancer types, no statistically significant differences in overall survival were found (p=0.878).*

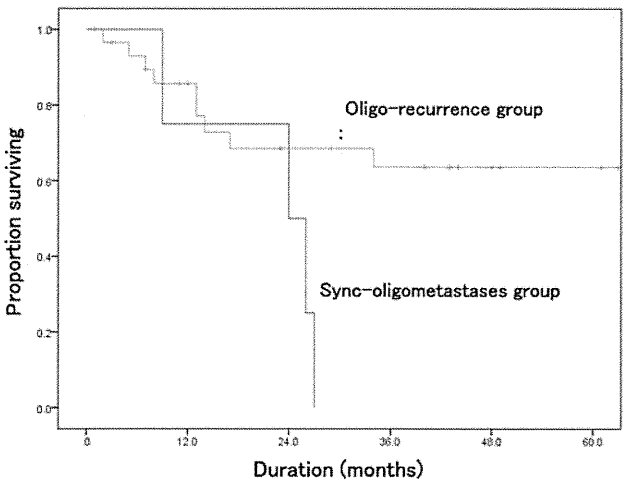

Figure 4. *Overall survival stratified by oligo-status. The 2-year overall survival rate for the oligo-recurrence group was 68.5% (95% confidence interval=50.3-86.7%), whereas that for the sync-oligometastases group was 50.0% (95% confidence interval=1.0-99.0%). This was statistically significant (p=0.037).*

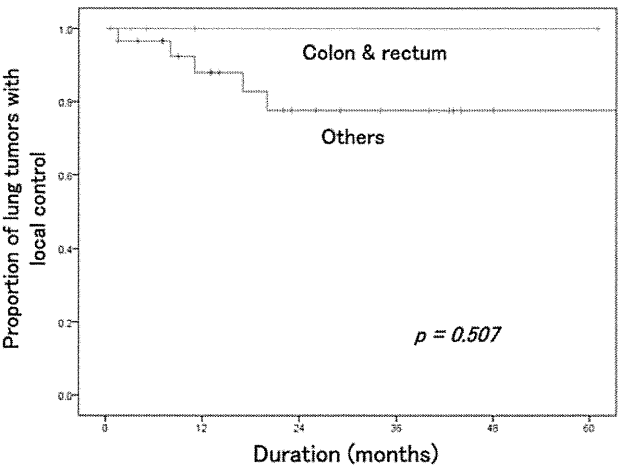

Figure 6. *Local control stratified by histopathology. Comparing patients with colon and rectal cancer to those with other cancer types, no statistically significant differences in local control were found (p=0.507).*

oligometastases and oligo-recurrence have attracted attention recently is that less-invasive local treatment modalities such as sophisticated thoracoscopic surgery, SBRT and radiofrequency ablation are now available. Therefore, the Japanese guidelines recommend resection whenever possible for pulmonary metastasis in the oligo-recurrence state, such as in the primary site of colorectal cancer (13).

The current study achieved a 2-year overall survival rate of 65.7% (95%CI=48.3-83.1%) for the whole patient group. This is promising, considering that all our patients had recurrent or metastatic disease. The 2-year local control rate for the whole group was 79.1% (95% CI=62.4-95.8%). This was also a good result. Even if there were too few cases of pulmonary oligometastases in this study to draw firm

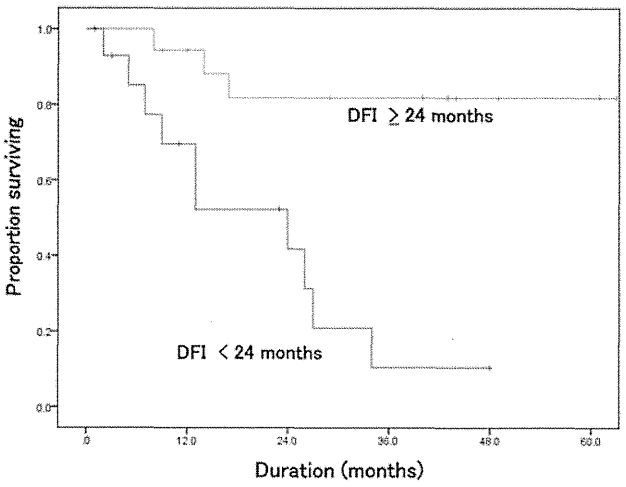

Figure 7. *Overall survival stratified by DFI. The 2-year overall survival rate of DFI ≥24 months was 81.9% (95% confidence interval=63.3%-100%), whereas that of DFI<24 months was 41.8% (95% confidence interval=12.8-70.8%). This was statistically significant (p<0.001)*

conclusions, it is suggested that SBRT should be performed, rather than no treatment or systemic therapy alone, in these situations. Systemic therapy alone, for recurrent or metastatic cancer, does not generally achieve a cure.

This is the key difference between SBRT and systemic therapy. SBRT and other local treatments can achieve a cure for patients with oligometastases, especially those with oligo-recurrence. When another recurrence occurs after SBRT, patients with oligo-recurrence can repeat SBRT, even if the metastatic tumor occurs in again in the lung. Onishi *et al*. recently gave an excellent case report about sequential oligo-recurrence (14).

However, it cannot be said that patients with oligometastases always have long-term survival with good quality of life and achieve a cure. From the results of stratification by status, the oligo-recurrence group achieved a significantly higher 2-year overall survival rate (68.5% vs. 50.0%; p=0.037). As shown herein, for patients with oligometastatic disease, controlling the primary tumor is very important. Primary lesions often invade neighboring tissues and are often associated with regional lymph node metastases. This is why control of primary lesions is more difficult than that of round- or oval-shaped recurrent or metastatic lesions. In addition, recurrent or metastatic lesions rarely lead to regional lymph node metastasis.

In terms of histopathology, recurrent or metastatic lesions originating from the colon and rectum were reported to have worse responses than those from other origins when these lesions were treated by SBRT (15). In the current study, recurrent or metastatic tumors originating from the colon and rectum did not show a statistically worse response than those of other origins. However, it is difficult to generalize from these findings as there were only 34 patients in the study, and there were only the cases of colon and rectum primary cancer.

A relationship between outcomes of oligometastases treated by SBRT and the DFI has been reported : a DFI of 39.1 months or more was reported to predict better prognosis than that of less than 39.1 months in the study of SBRT for pulmonary oligo-recurrence (16). In another study, a DFI of 36 months or more was associated with better prognosis than that of one of less than 36 months (17). The threshold of the current study DFI was set at 24 months. A DFI of 24 months or more led to a 2-year overall survival rate of 81.9% versus 41.8% for a DFI of less than 24 months. These results were comparable to those of previous reports. A long DFI was found to be associated with a good prognosis. In addition, it was reported that certain interleukin molecules were involved when new distant recurrences or metastases arose from a disease-free state (7).

Conclusion

SBRT for pulmonary oligometastases achieved good results and there were no serious adverse events among 34 patients. However, a prospective study is required to validate these results. For such a study, we recommend that registered patients should be limited to those with oligo-recurrence due to their better prognosis compared to those with sync-oligometastases. Other findings in the current study confirmed that a long DFI (≥24 months) was a favorable prognostic factor for patients with pulmonary oligometastases.

Conflicts of Interest

The Authors declare that they have no competing interests.

Acknowledgements

This study was supported partly by grant-in-aid from JSPS KAKENHI Grant Number 21791209 and 25461926.

References

1 Hellman S and Weichselbaum RR: Oligometastases. J Clin Oncol *13*: 8-10, 1995.

2 Niibe Y, Nakano T, Ohno T, Suzuki Y, Oka K and Tsujii H: Prognostic significance of c-erbB-2/HER2 expression in advanced uterine cervical carcinoma with para-aortic lymph node metastasis treated with radiation therapy. Int J Gynecol Cancer *13*: 849-855, 2003.

3 Niibe Y, Kazumoto T, Toita T, Yamazaki H, Higuchi K, Ii N, Suzuki K, Uno T, Tokumaru S, Takayama M, Sekiguchi K, Matsumoto Y, Michimoto K, Oguchi M and Hayakawa K: Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan:a multi-institutional study. Gynecol Oncol *103*: 435-438, 2006.

4 Niibe Y, Kenjo M, Kazumoto T, Michimoto K, Takayama M, Yamauchi C, Kataoka M, Suzuki K, Ii N, Uno T, Takanaka T, Higuchi K, Yamazaki H, Tokumaru S, Oguchi M and Hayakawa K: Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5000. Int J Radiat Oncol Biol Phys *66*: 1366-1369, 2009.

5 Niibe Y, Karasawa K, Nakamura O, Shinoura N, Okamoto K, Yamada R, Fukino K and Tanaka Y: Survival benefit of stereotactic radiosurgery for metastatic brain tumors in patients with controlled primary lesions and no other distant metastases. Anticancer Res *23*: 4157-4160, 2003.

6 Niibe Y and Hayakawa K: Oligometastases and oligo-recurrence:the new era of cancer therapy. Jpn J Clin Oncol *40*: 107-110, 2010.

7 Niibe Y and Chang JY. Novel insights of oligometastases and oligo-recurrence and review of the literature. Pulm Med *2012*: 261096, 2012.

8 Sole CV, Calvo FA, Lizarraga S, Gonzalez-Bayon L, Segundo CG, Desco M and Garcia-Sabrido JL: Single-institution multidisciplinary management of locoregional oligo-recurrent pelvic malignancies: long-term outcome analysis. An Surg Oncol in press.

9 Takahashi W, Nakajima M, Yamamoto N, Yamada S, Yamashita H, Nakagawa K, Tsuji H and Kamada T: Carbon ion radiotherapy for oligo-recurrent lung metastases from colorectal cancer: a feasibility study. Radiat Oncol *9*: 68, 2014.

10 Huang F, Wu G and Yang K: Oligometastasis and oligo-recurrence: more than a mirage. Radiat Oncol 9: 230, 2014.

11 http://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx

12 Long-term results of lung metastasectomy:prognostic analyses based on 5206 cases: The International Registry of Lung Metastases. J Thorac Cardiovasc Surg *113*: 37-49, 1997.

13 Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K and Sugihara K: Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) gudelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol *17*: 1-29, 2012.

14 Onishi H, Ozaki M, Kuriyama K, Komiyama T, Marino K, Araya M, Saito R, Aoki S, Maehata Y, Tominaga L, Oguri M, Watanabe I, Onohara K, Watanabe M, Sano N and Araki T: Stereotactic body radiotherapy for metachronous multisite oligo-reccurrence:a long-surviving case with sequential oligo-recurrence in four different organs treated using locally radical radiotherapy and a review of the literature. Pulm Med *2012*: 713073, 2012.

15 Takeda A, Kunieda E, Ohashi T, Aoki Y, Koike N and Takeda T: Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. Radiother Oncol *101*: 255-259, 2011.

16 Takahashi W, Yamashita H, Niibe Y, Shiraishi K, Hayakawa K and Nakagawa K: Stereotactic body radiotherapy for metastatic lung cancer as oligo-recurrence: an analysis of 42 cases. Pulm Med *2012*: 454107, 2012.

17 Inoue T, Katoh N, Onimaru R and Shirato H: Clinical outcomes of stereotactic body radiotherapy for patients with lung tumors in the state of oligo-recurrence. Pulm Med *2012*: 369820, 2012.

Received May 5, 2015
Revised June 13, 2015
Accepted June 15, 2015

Japanese Journal of Clinical Oncology Advance Access published May 15, 2015

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2015, 1–8
doi: 10.1093/jjco/hyv069
Original Article

Original Article

Are hospitals in Japan with larger patient volume treating younger and earlier-stage cancer patients? An analysis of hospital-based cancer registry data in Japan

Yoichiro Tsukada[1,2,*], Fumiaki Nakamura[3], Momoko Iwamoto[1], Hiroshi Nishimoto[4], Yoshiko Emori[4], Atsuro Terahara[2], and Takahiro Higashi[1]

[1]Division of Health Services Research, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, [2]Department of Radiology, Toho University Omori Medical Center, Tokyo, [3]Department of Public Health/Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, and [4]Division of Surveillance, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

*For reprints and all correspondence: Yoichiro Tsukada, Division of Health Services Research, Center for Cancer Control and Information Services, National Cancer Center, Japan 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: yotsukad@ncc.go.jp

Received 6 January 2015; Accepted 10 April 2015

Abstract

Objective: Differences in hospital case-mix have not been adequately accounted for in hospital volume and patient outcome studies in Japan. We aimed to examine whether differences may exist by investigating the distribution of patients' stage and age across designated cancer treatment hospitals of varying patient volume across Japan.

Methods: We analyzed data of gastric, breast, colorectal, lung and liver cancer patients who were included in the national database of hospital-based cancer registries between 2008 and 2011. We investigated the association between hospital volume, cancer stage and patient age. Hospitals were classified into five groups according to patient volume.

Results: In total, 676 713 patients met the inclusion criteria. The proportion of patients with early-stage (tumor–node–metastasis Stage 0 or I) cancer was higher among high-volume hospitals for all cancer types except small cell lung cancer. The proportion of older patients (age >75 years) was smaller among high-volume hospitals for all cancer types. The difference in the proportion of patients with early-stage cancers between very low-volume and very high-volume hospitals was greatest for non-small cell lung cancer (26.5% for very low and 43.5% for very high). This difference for the proportion of older patients was also greatest for non-small cell lung cancer (48.9% for very low and 30.3% for very high).

Conclusions: We showed that the proportions of early-stage cancer patients and younger patients are greater in higher-volume hospitals compared with lower-volume hospitals in Japan. Researchers conducting volume–outcome studies and policymakers analyzing hospital performance should be cautious when making interhospital comparisons.

Key words: aged, high-volume hospitals, low-volume hospitals, neoplasm staging, treatment outcome

Introduction

The association between hospital volume and patient outcomes, such as mortality and length of hospital stay, is of considerable interest not only to patients and healthcare professionals but also to hospital administrators and policymakers, whose duty is to improve the care of patients and allocate appropriate resources to hospitals within community healthcare systems. Various studies on hospital volume and patient outcomes demonstrate that patients who receive cancer care or procedures at high-volume centers tend to perform better, both in short- and long-term outcomes (1–6). However, results of volume–outcome studies must be interpreted with caution because they are prone to residual confounding, which is common when comparing hospital performance (7,8).

To make risk adjustments in mortality across hospitals, researchers often adjust for patient characteristics that may differ across institutions. For instance, Finks et al. (4) adjusted for patient age, sex, race, type of hospital admission (elective, urgent or emergency), comorbidities and socioeconomic status when comparing 30 day mortality for lung, esophageal, pancreatic and bladder cancer surgeries across hospitals of various hospital volume. Huo et al. (5) used propensity score matching to adjust for baseline mortality risk of metastatic melanoma patients across hospitals with varying caseloads. These adjustments are intended to address differences in case-mix of comorbid conditions and socioeconomic factors across various hospitals, and in doing so, conclude that the observed effects are not due to differences in these characteristics, but in some aspects of care that is provided in high-volume hospitals.

However, statistical adjustments are not perfect. Risk adjustments cannot fully compensate for interhospital variability when adjustments do not cover all important confounders, when sample size is small, or when characteristics of hospitals differ greatly (7,8). In Japan, cancer care hospitals range from small community hospitals, which treat various medical conditions; to medium-volume hospitals, which provide tertiary emergency services; and to larger university teaching hospitals and cancer research centers, where many clinical trials are conducted. Descriptive statistics from volume–outcome studies in Japan show that the mean age and stage of cancer patients are greater in low-volume hospitals compared with high-volume hospitals, supporting the idea that differences in patient population exist by hospital type and volume (9–12). Therefore, it is possible that high-volume hospitals are primarily treating younger and less-complex cases, whereas lower-volume hospitals are treating older patients, who may have more comorbidities, may be frailer, and may be more likely to develop complications. As yet, no study has investigated this issue. More fundamentally, we do not even know whether differences in basic patient characteristics, such as patient age and disease stage, exist by hospital volume across cancer care hospitals in Japan.

As a first step in understanding if these investigations should be pursued in the future so that more thorough risk adjustments, such as comorbidities and socioeconomic factors, should be done when making interhospital comparisons of cancer care performance in Japan, we studied the differences in the age and stage of gastric, breast, colorectal, lung and liver cancer patients among hospitals with different patient volumes, using hospital-based cancer registry data from 2008 to 2011.

Patients and methods

Database and study hospitals

We analyzed data of cancer patients included in the hospital-based cancer registry (HBCR) from 2008 to 2011. HBCR has been collecting demographic and diagnostic data of new cancer patients diagnosed, treated or followed up at designated cancer care hospitals (DCCHs) across Japan since 2007. They cover ~70% of all cancer incidence in 2011 (13). These hospitals are designated by the Ministry of Health, Labour and Welfare to provide specialized cancer care across communities in Japan, and they are required to submit their registry data to the National Cancer Center on an annual basis. The number of DCCHs that submitted data increased from 358 in 2008 to 370, 385 and 395 in 2009, 2010 and 2011, respectively. The registry database contains information on age and sex of patients as well as detailed clinical information, such as the following: clinical and pathological tumor–node–metastasis (TNM) stages; topology (site); histology codes of The International Classification of Diseases for Oncology, third edition (ICD-O-3); dates of diagnosis and treatment; and modalities used for the patients' first course of treatment. This information is collected by tumor registrars, who have completed training courses organized by the National Cancer Center, and subsequently undergoes data quality checks. Because some DCCHs do not receive a designation every year and may not have submitted registry data to the National Cancer Center for those years, we limited our analyses to hospitals that submitted registry data for all four years during the study period (2008–11).

This study was approved by the institutional review board of the National Cancer Center, Japan, number 2013–151.

Target patients

We extracted the data of patients who were diagnosed with gastric cancer (ICD-O-3 morphology: C16.0–16.9), breast cancer (C50.0–50.9), colorectal cancer (C18.0–20.9), liver cancer (C22.0) and lung cancer (C34.0–34.9). Lung cancer was further divided into small cell cancer (ICD-O-3 histology code 8041–8045) and non-small cell cancer (excluding histology codes 8041–8045). We excluded patients with atypical histology according to the ICD-O-3 codes, small cell carcinoma (8041–8045) occurring at sites other than the lung, pancreatic endocrine tumors (8150–8157), carcinoid tumors (8240–8249), specialized gonadal neoplasms (8590–8671), paragangliomas and glomus tumors (8680–8713), nevi and melanomas (8720–8790), soft tissue tumors and sarcomas (8800–8806), fibromatous neoplasms (8810–8836), mixomatous neoplasms (8840–8842), lipomatous neoplasms (8850–8881), myomatous neoplasms (8890–8921), complex mixed and stromal neoplasms (8930–8991), synovial-like neoplasms (9040–9044), germ cell neoplasms (9060–9091), trophoblastic neoplasms (9100–9105), mesonephromas (9110), blood vessel tumors and lymphatic vessel tumors (9120–9175), osseous and chondromatous neoplasms (9180–9252), giant cell tumors (9250–9252), miscellaneous bone tumor (9260–9262), odontogenic tumors (9270–9342), nerve sheath tumors (9540–9571), lymphomas and hematological malignancies (9590–9989) and male breast cancer patients. We also excluded from our analysis patients who received endoscopic resection alone as their method of cancer treatment. Including these patients would have made hospitals with large caseloads of endoscopic resections appear to have a higher proportion of early-stage patients, while excluding these patients allowed us to obtain a conservative estimate for the relationship between hospital volume and cancer stage.

Definition of cancer stage and hospital classification

HBCR uses Union for International Cancer Control (UICC) TNM codes (UICC TNM classification of malignant tumors, 6th edition) to record cancer stages, except for liver cancer, which are staged using the Japanese staging standard (the General Rules for the Clinical

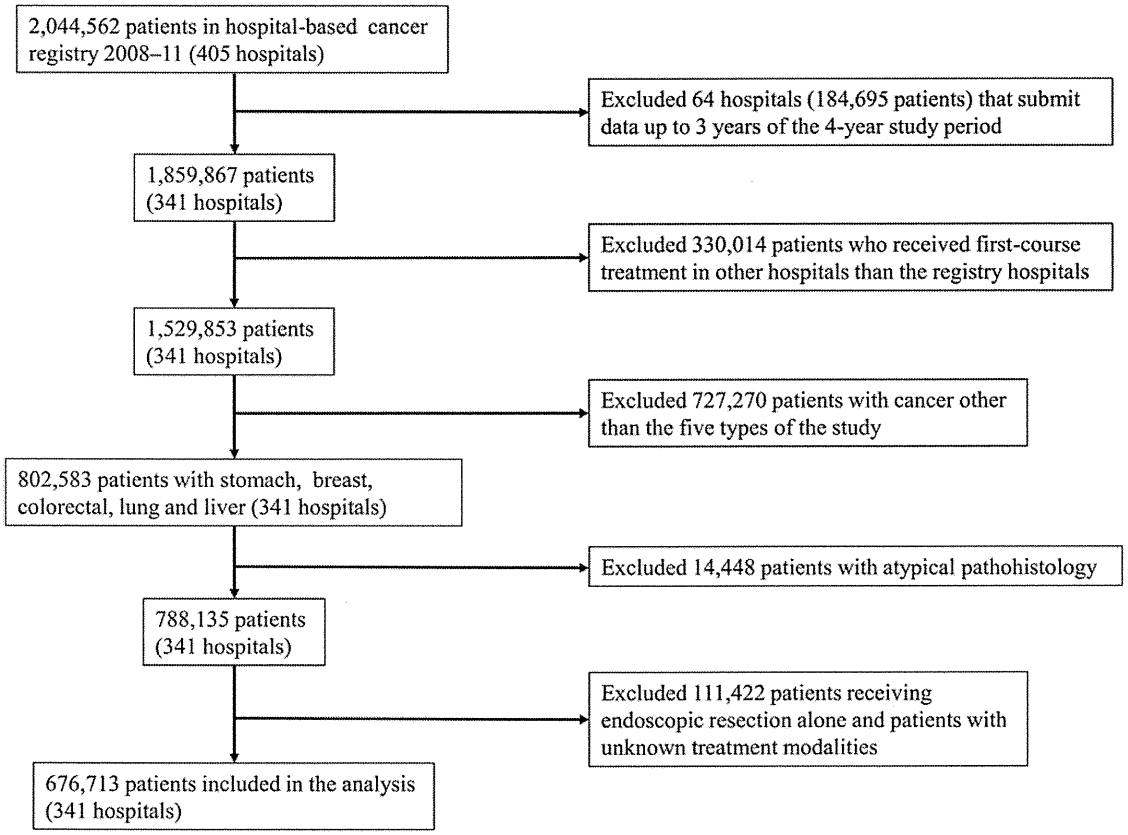

Figure 1. Flowchart of included and excluded patients from the hospital-based cancer registry data in the study.

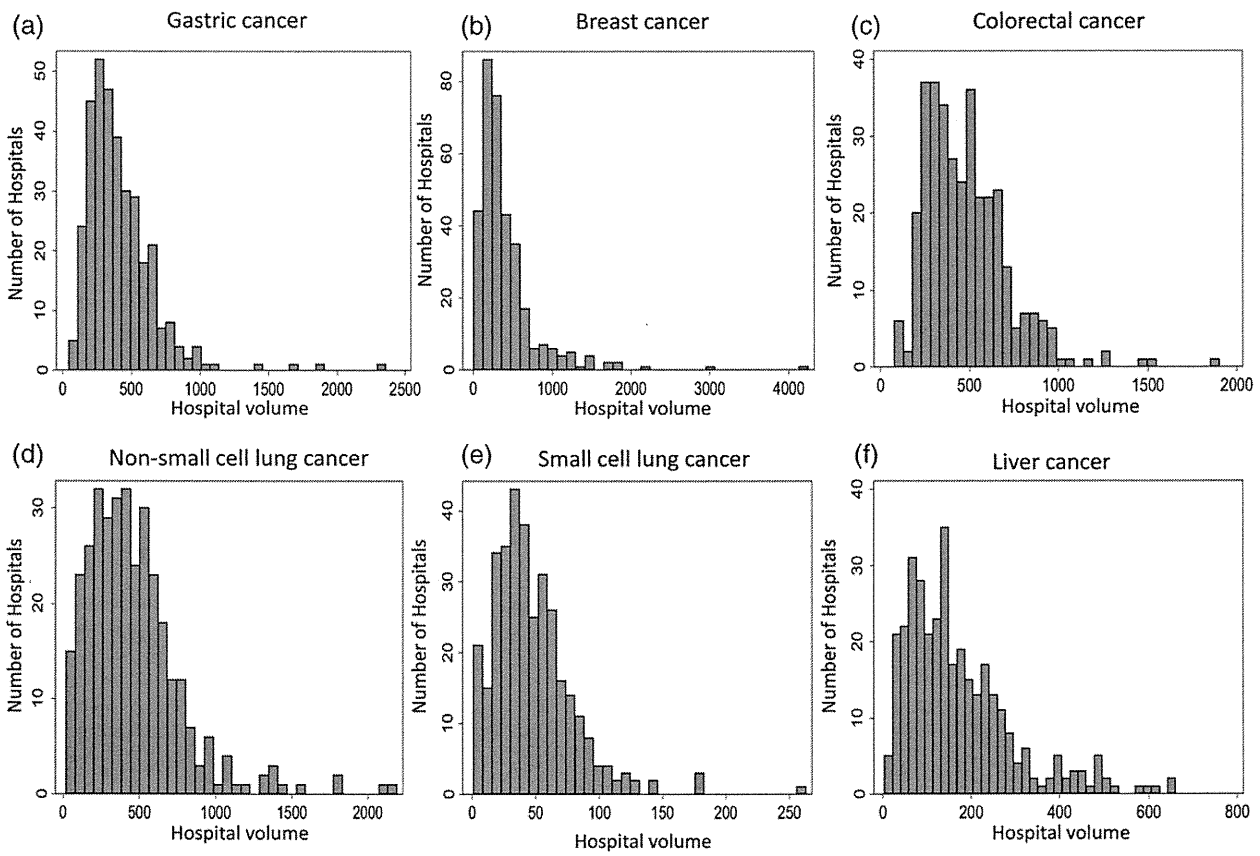

Figure 2. Histograms of the distributions of hospital volumes. The histograms juxtapose hospital volume of each hospital among the designated cancer care hospitals.

and Pathological Study of Primary Liver Cancer, 5th edition, revised version) (14). We used clinical stages of disease as the patients' final stage when pathological stages were not available.

We defined hospital volume by quintiles using the total number of patients registered from 2008 to 2011 for each type of cancer: very low volume (the lowest quintile), low volume, middle volume, high volume and very high volume (the highest quintile).

Statistical analyses

The associations between (i) hospital volume and the percentage of patients with Stage 0 or I disease and (ii) hospital volume and the percentage of patients aged >75 years, were evaluated using one-way analysis of variance (ANOVA). We used the Kruskal–Wallis test when the normality and equal variance assumptions of ANOVA did not hold. Patients with unknown stages were excluded from the first analysis (proportion of patients with Stage 0 or I cancer). All tests for significance were two-tailed, with an α-value set at 0.05. Stata® version 13.1 software (StataCorp, College Station, TX) was used for statistical analyses.

Results

A total of 676 713 patients treated at 341 DCCHs from 2008 to 2011 were included in the analysis. Figure 1 shows the flow chart for selecting the analytical dataset from the HBCR. While all 676 713 patients entered the analysis of hospital volume and patient age, 9425 patients (1.4%) were excluded from the volume–stage analysis due to unknown stages. Figure 2 shows the distributions of hospital volume across DCCHs. They were generally skewed to the right, primarily for breast cancer.

Demographic characteristics of patients in the analyses by hospital volume are shown in Table 1. Breast cancer patients were the youngest (mean age ± standard deviation 60.7 ± 3.3 years) and non-small cell lung cancer patients were the oldest (70.9 ± 2.2 years).

Hospital volume and cancer stages

The associations between hospital volume and the proportion of patients with each cancer stage and early stage cancers (Stage 0 or I) according to cancer type are shown in Table 2 and Figure 3. The proportion of patients with early stage cancer increased as hospital

Table 1. Characteristics of patient groups by hospital volume

	Total	Very low-volume hospitals	Low-volume hospitals	Medium-volume hospitals	High-volume hospitals	Very high-volume hospitals
Gastric cancer						
Number of hospitals, *n*	341	70	67	68	68	68
Mean number of patients in each hospital, *n* (range)	141,422	178 (45–229)	272 (231–317)	362 (318–407)	485 (410–563)	779 (566–2358)
Age, mean (SD[a]) (years)	69.4 (2.0)	70.6 (2.1)	70.3 (1.5)	69.6 (1.6)	68.9 (1.6)	68.0 (1.8)
Sex male, mean (SD[a]) (%)	69.1 (3.1)	68.5 (3.9)	69.0 (3.3)	69.6 (2.7)	68.7 (2.8)	69.5 (2.5)
Breast cancer						
Number of hospitals, *n*	341	69	69	68	67	68
Mean number of patients in each hospital, *n* (range)	137,899	99 (4–153)	195 (154–243)	295 (244–357)	443 (359–554)	998 (556–4243)
Age, mean (SD[a]) (years)	60.7 (3.3)	64.5 (3.5)	61.6 (2.0)	60.7 (1.9)	59.3 (1.6)	57.4 (1.9)
Sex male, mean (SD[a]) (%)	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]
Colorectal cancer						
Number of hospitals, *n*	341	69	68	69	67	68
Mean number of patients in each hospital, *n* (range)	164,772	227 (78–284)	333 (286–382)	449 (385–505)	574 (506–647)	839 (652–1902)
Age, mean (SD[a]) (years old)	69.6 (2.0)	70.6 (2.2)	70.3 (1.6)	69.8 (1.7)	69.2 (1.8)	68.2 (2.0)
Sex male, mean (SD[a]) (%)	57.8 (3.5)	57.4 (4.1)	57.6 (3.8)	57.7 (3.7)	58.0 (3.1)	58.5 (2.3)
Non-small cell lung cancer						
Number of hospitals, *n*	341	69	68	68	68	68
Mean number of patients in each hospital, *n* (range)	158,064	127 (20–214)	281 (215–344)	410 (346–479)	561 (488–654)	943 (656–2194)
Age, mean (SD[a]) (years)	70.9 (2.2)	73.2 (2.4)	71.8 (1.5)	70.5 (1.5)	69.9 (1.2)	68.9 (1.4)
Sex male, mean (SD[a]) (%)	69.2 (4.5)	71.4 (5.8)	69.5 (4.2)	69.3 (3.6)	68.6 (3.4)	67.1 (4.3)
Small cell lung cancer						
Number of hospitals, *n*	338	70	72	62	69	65
Mean number of patients in each hospital, *n* (range)	16,045	13 (1–22)	30 (23–36)	42 (37–48)	59 (49–69)	97 (70–263)
Age, mean (years)	70.5 (2.5)	71.7 (3.9)	70.9 (1.8)	70.6 (1.9)	70.0 (1.8)	69.2 (1.6)
Sex male, mean (SD[a]) (%)	83.6 (7.8)	84.2 (12.7)	83.1 (6.6)	84.9 (6.1)	82.9 (5.4)	82.9 (5.4)
Liver cancer						
Number of hospitals, *n*	341	69	69	67	69	67
Mean number of patients in each hospital, *n* (range)	58,511	47 (4–72)	95 (73–118)	143 (120–170)	210 (171–252)	369 (253–661)
Age, mean (SD[a]) (years)	70.4 (1.7)	71.1 (2.1)	70.9 (1.6)	70.8 (1.4)	70.0 (1.3)	69.3 (1.3)
Sex male, mean (SD[a]) (%)	69.7 (5.7)	70.8 (7.2)	68.9 (7.0)	69.4 (5.3)	69.5 (4.5)	69.8 (3.6)

[a]Standard deviation.

[b]Not applicable.

volume increased for all cancer types except for small cell lung cancer. This trend was prominent in breast cancer (proportion of early stage cancer patients increased from 42.1% in very low-volume hospitals to 51.9% in very high-volume hospitals), non-small cell lung cancer (26.5–43.5%) and liver cancer (26.1–31.7%). However, this trend was less prominent for gastric (46.4–51.2%) and colorectal cancers (24.3–26.2%). These differences between very low-volume and very high-volume hospitals were greatest (17.0% difference) for non-small cell lung cancer.

Hospital volume and age

The associations between hospital volume and the proportion of patients aged >75 years (older patients) according to cancer type are shown in Table 3 and Figure 4. For all cancer types, the proportion

Table 2. Proportion of patients with each cancer stage by volume-based groups

	Proportion of patients with each cancer stage, mean (standard deviation) (%)					
	Very low-volume hospitals	Low-volume hospitals	Middle-volume hospitals	High-volume hospitals	Very high-volume hospitals	*P* value
Gastric cancer						
Stage 0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Stage I	45.1 (6.5)	45.8 (5.4)	48.0 (5.7)	49.4 (5.7)	50.3 (5.4)	
Stage II	11.2 (3.2)	10.9 (2.5)	10.8 (2.1)	10.6 (2.0)	10.4 (1.3)	
Stage III	10.7 (3.6)	10.8 (3.2)	10.5 (2.4)	10.3 (2.3)	10.2 (1.9)	
Stage IV	30.0 (5.7)	30.6 (4.5)	29.0 (4.1)	27.7 (4.5)	27.3 (4.1)	
Unknown stage	3.0 (3.0)	1.9 (1.8)	1.7 (1.4)	1.9 (1.8)	1.8 (1.5)	
Stage 0 or I[a]	46.4 (6.2)	46.7 (5.4)	48.8 (5.7)	50.4 (5.6)	51.2 (5.3)	<0.001*
Breast cancer						
Stage 0	6.2 (4.1)	8.9 (4.5)	10.1 (3.7)	12.1 (4.3)	13.9 (3.9)	
Stage I	35.6 (8.9)	38.8 (6.6)	37.9 (5.3)	38.6 (5.0)	37.7 (4.5)	
Stage II	37.5 (11.8)	33.8 (6.7)	34.6 (5.8)	33.5 (6.3)	33.8 (4.3)	
Stage III	12.9 (6.2)	12.1 (3.3)	11.2 (3.1)	10.7 (2.7)	10.1 (2.8)	
Stage IV	7.1 (3.9)	5.5 (2.1)	5.5 (1.9)	4.6 (1.5)	3.9 (1.4)	
Unknown stage	0.7 (1.1)	0.8 (1.2)	0.7 (0.7)	0.5 (0.6)	0.6 (0.9)	
Stage 0 or I[a]	42.1 (10.5)	48.0 (6.9)	48.3 (6.4)	51.0 (7.4)	51.9 (6.0)	<0.001**
Colorectal cancer						
Stage 0	4.5 (2.8)	4.9 (2.3)	4.7 (2.5)	4.9 (2.0)	5.2 (2.3)	
Stage I	19.4 (4.0)	18.6 (4.2)	20.1 (3.1)	20.4 (3.2)	20.8 (2.7)	
Stage II	27.3 (4.5)	27.5 (3.8)	27.7 (3.4)	27.8 (2.8)	26.9 (3.0)	
Stage III	25.4 (4.1)	26.9 (3.8)	25.9 (3.2)	25.7 (2.7)	26.8 (2.3)	
Stage IV	22.0 (4.4)	20.4 (3.5)	20.0 (3.4)	20.1 (3.2)	19.2 (2.8)	
Unknown stage	1.4 (1.4)	1.6 (1.4)	1.5 (1.6)	1.0 (0.7)	1.1 (1.2)	
Stage 0 or I[a]	24.3 (4.6)	23.9 (4.6)	25.2 (3.8)	25.6 (3.9)	26.2 (3.3)	0.002**
Non-small cell lung cancer						
Stage 0	0.1 (0.3)	0.1 (0.3)	0.2 (0.4)	0.1 (0.4)	0.2 (0.3)	
Stage I	25.6 (15.9)	32.3 (9.0)	38.7 (8.8)	40.0 (8.5)	42.9 (9.2)	
Stage II	6.0 (3.2)	6.0 (1.7)	6.5 (1.3)	6.9 (1.6)	7.1 (1.5)	
Stage III	25.1 (7.6)	25.7 (5.4)	24.0 (4.4)	23.7 (3.6)	22.4 (3.8)	
Stage IV	38.7 (11.7)	33.7 (7.1)	29.1 (6.1)	27.9 (6.6)	26.3 (6.0)	
Unknown stage	4.5 (5.1)	2.3 (2.4)	1.6 (1.9)	1.3 (1.4)	1.1 (1.5)	
Stage 0 or I[a]	26.5 (15.6)	33.1 (9.1)	39.5 (8.7)	40.6 (8.5)	43.5 (9.1)	<0.001**
Small cell lung cancer						
Stage 0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Stage I	8.5 (13.9)	7.8 (5.2)	9.3 (6.9)	6.6 (4.0)	7.9 (3.8)	
Stage II	4.5 (6.6)	5.0 (4.5)	5.7 (3.8)	5.3 (3.1)	6.2 (3.3)	
Stage III	33.6 (18.7)	35.5 (10.7)	35.0 (7.4)	35.5 (7.4)	35.4 (5.2)	
Stage IV	51.2 (17.0)	50.1 (10.7)	48.5 (8.3)	51.0 (8.8)	49.6 (7.2)	
Unknown stage	2.3 (5.3)	1.6 (3.4)	1.4 (1.9)	1.7 (2.6)	0.9 (1.6)	
Stage 0 or I[a]	8.6 (13.9)	8.0 (5.2)	9.4 (6.9)	6.7 (4.1)	8.0 (3.8)	0.013**
Liver cancer						
Stage 0	– (–)	– (–)	– (–)	– (–)	– (–)	
Stage I	24.3 (11.4)	29.2 (9.2)	29.5 (8.2)	29.0. (7.0)	31.3 (6.0)	
Stage II	28.5 (8.9)	30.4 (6.9)	32.8 (5.7)	32.6 (5.5)	34.1 (4.2)	
Stage III	20.9 (8.2)	20.0 (6.2)	21.6 (5.5)	21.6 (4.4)	21.4 (4.3)	
Stage IV	19.3 (9.4)	15.6 (5.3)	14.1 (5.0)	14.1 (4.4)	11.8 (3.6)	
Unknown stage	7.1 (10.8)	4.8 (8.0)	2.0 (2.6)	2.6 (6.3)	1.5 (2.4)	
Stage 0 or I[a]	26.1 (12.0)	30.6 (9.3)	30.1 (8.2)	29.8 (6.8)	31.7 (6.1)	0.002**

*One-way analysis of variance (ANOVA).

**Kruskal–Wallis test.

[a]Excluding patients with unknown cancer stage.

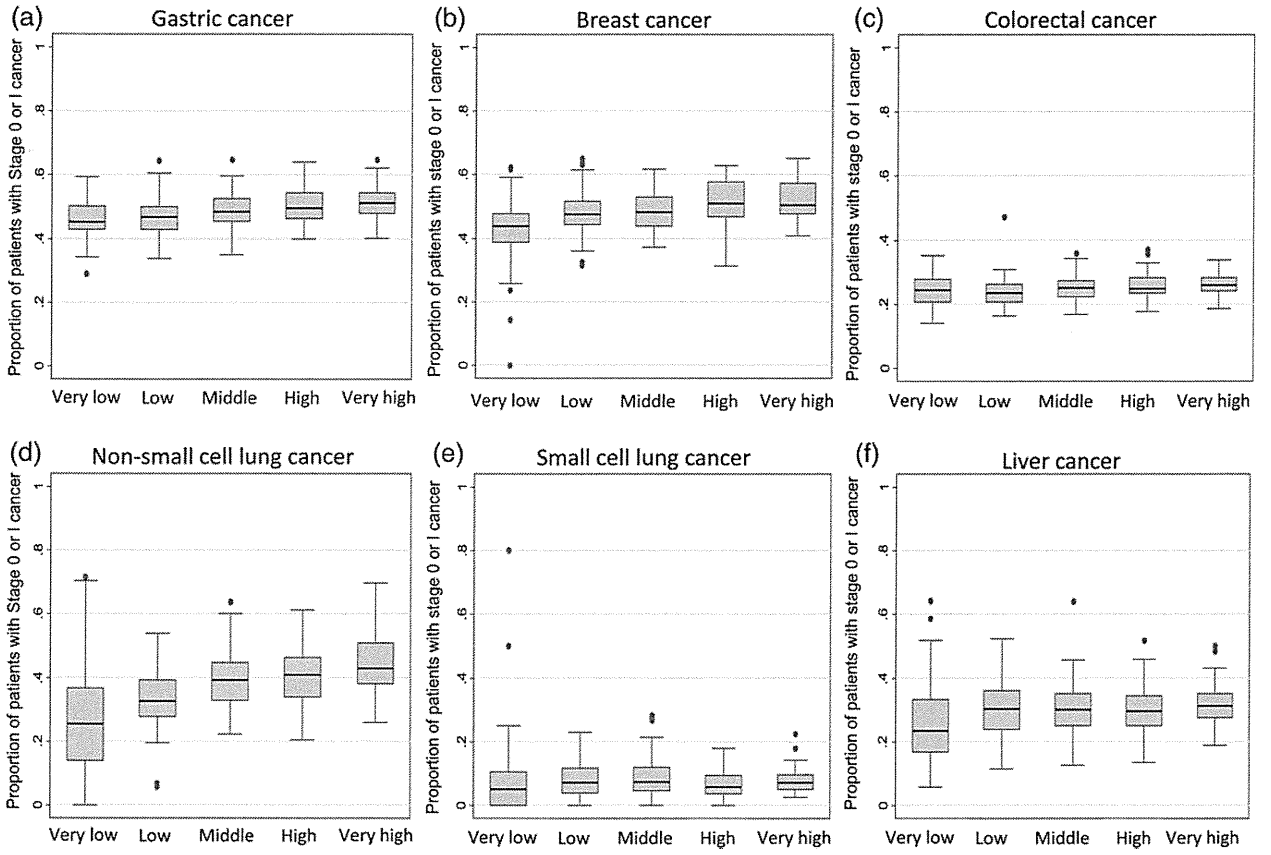

Figure 3. Associations between hospital volume and proportion of patients with Stage 0 or I cancer. Box and whisker plots, showing the relationship between the proportions of patients with Stage 0 or I cancer and hospital volume in (a) gastric cancer, (b) breast cancer, (c) colorectal cancer, (d) non-small cell lung cancer, (e) small cell lung cancer and (f) liver cancer. On the *x* axis, hospital volume increases from left to right, from 'very low', 'low', 'middle', 'high' and 'very high', with the abbreviations representing very low-volume hospitals, low-volume hospitals, medium-volume hospitals, high-volume hospitals and very high-volume hospitals, respectively. Boxes represent median and interquartile range (IQR) and whiskers represent ±1.5 IQR; filled circle denotes outliers.

Table 3. Proportion of patients aged >75 years by hospital volume

	Proportion of patients aged >75 years, mean (standard deviation) (%)					
	Very-low-volume hospitals	Low-volume hospitals	Medium-volume hospitals	High-volume hospitals	Very-high-volume hospitals	*P* value
Gastric cancer	38.6 (7.5)	37.1 (6.3)	34.8 (6.2)	32.7 (6.3)	29.2 (6.6)	<0.001*
Breast cancer	25.4 (9.7)	18.3 (4.4)	16.3 (3.8)	13.6 (3.0)	10.4 (3.5)	<0.001**
Colorectal cancer	39.0 (7.7)	37.2 (5.9)	35.2 (6.3)	33.3 (6.9)	30.0 (7.0)	<0.001*
Non-small cell lung cancer	48.9 (11.3)	42.9 (6.5)	37.4 (7.3)	34.4 (5.3)	30.3 (6.0)	<0.001**
Small cell lung cancer	38.9 (10.9)	36.5 (10.0)	35.0 (10.3)	32.4 (9.3)	27.7 (7.6)	<0.001**
Liver cancer	38.3 (0.9)	37.6 (6.2)	37.2 (7.1)	34.4 (5.0)	31.7 (4.8)	<0.001**

*One-way ANOVA.
**Kruskal–Wallis test.

of patients aged >75 decreased as hospital volume increased. For gastric cancer, the proportion of older patients was 38.6% in very low-volume hospitals, but 29.2% in very high-volume hospitals. For breast cancer, the proportion was 25.4% for very low-volume hospitals and 10.4% for very high-volume hospitals. These figures were 39.0 and 30.0% for colorectal cancer, 48.9 and 30.3% for non-small cell lung cancer, 38.9 and 27.7% for small cell lung cancer and 38.3 and 31.7% for liver cancer. Differences in the proportion of older patients between very low-volume and very high-volume hospitals were greatest for non-small cell lung cancer (18.6% difference).

Discussion

Our study showed that higher-volume hospitals in Japan treat a larger proportion of early-stage gastric, breast, colorectal, liver and

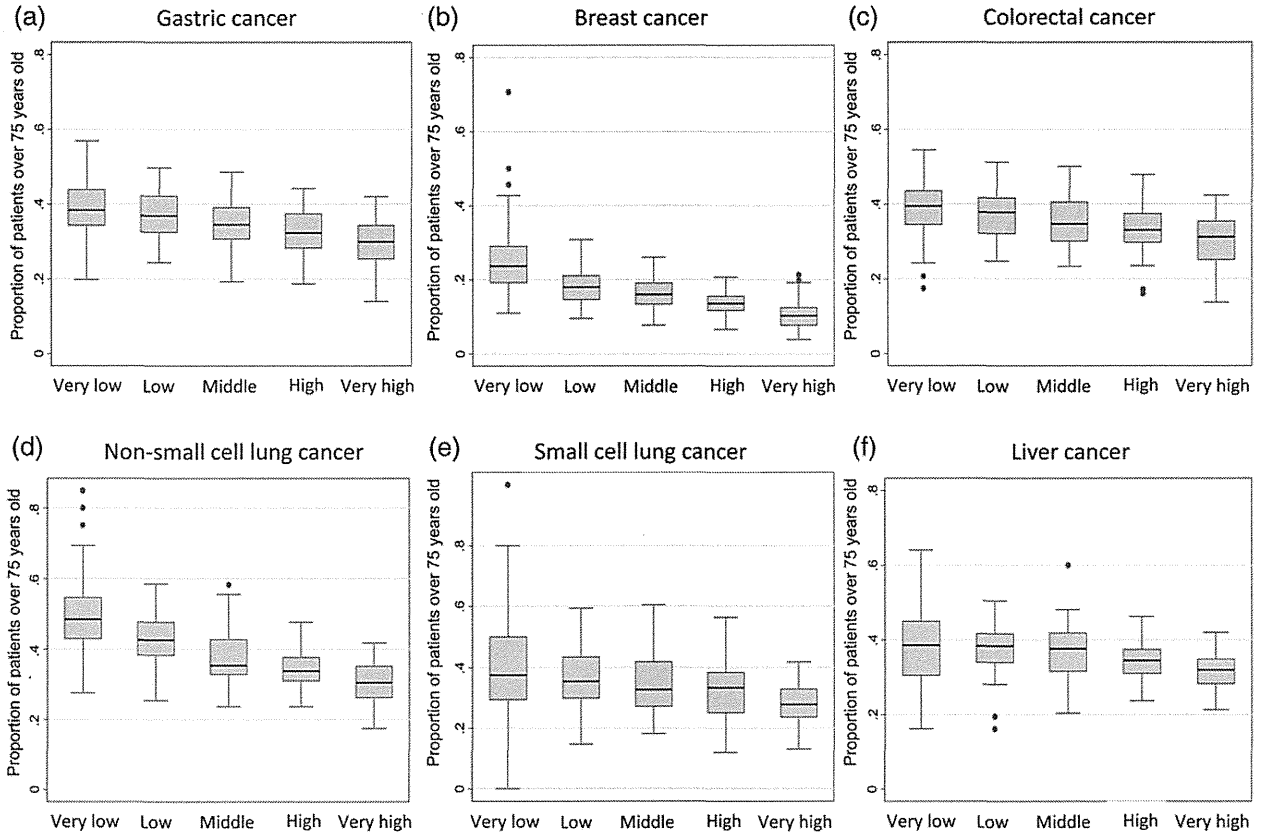

Figure 4. Associations between hospital volume and the proportion of patients aged >75 years. Box and whisker plots, showing the relationship between mean age of cancer patients and hospital volume in (a) gastric cancer, (b) breast cancer, (c) colorectal cancer, (d) non-small cell lung cancer, (e) small cell lung cancer and (f) liver cancer.

non-small cell lung cancer patients. In addition, high-volume hospitals treat a smaller proportion of patients aged >75 years with gastric, breast, colorectal, lung and liver cancers. Although we did not assess the overall health status of patients, including the presence of comorbidities, socioeconomic factors or lifestyle behaviors, our findings, which showed that high-volume hospitals are treating a greater proportion of younger and earlier-stage patients, raise the question that high-volume hospitals may be treating less-complex cases.

Our findings have two major implications. First, they add to the difficulty in examining volume–outcome relationships in Japan. Several studies conducted in two regions of Japan have shown that patient outcomes are better in higher-volume hospitals than in lower-volume hospitals (9–12). This is consistent with reports from other countries, which showed that long- and/or short-term outcomes were superior at high-volume hospitals for various types of cancers, including gastric cancer (15), colorectal cancer (6), esophageal cancer (16), breast cancer (3), lung cancer (1) and pancreatic cancer (17). However, the presence of comorbidities and socioeconomic factors can confound the relationship between hospital volume and outcomes (18). If our study findings are indicative of a general tendency among high-volume hospitals to treat less-complex cases than low-volume hospitals, what we have observed in volume–outcome studies in Japan can simply be explained by healthier patients having better outcomes.

Few studies have investigated the relationship between hospital volume and patient outcomes while accounting for a wide range of potentially confounding factors, including cancer stage, patient age, comorbidities and socioeconomic status. Zhan et al. (19) investigated the relationship between hospital volume and 30-day hospital mortality rate for Stage I–III colorectal cancer patients after adjusting for all of these factors. Zhan et al. showed that hospitals with higher surgical volume were treating a smaller proportion of patients who were at high risk of having poorer outcomes due to older age, advanced stage, multiple comorbidities and lower socioeconomic status compared with hospitals with lower surgical volume. Even after adjusting for hospital effects, these factors had a strong confounding effect on 30-day hospital mortality. Although we must wait for further studies to make any conclusions, a similar pattern of care may occur among cancer treatment hospitals in Japan.

The second implication of our findings is for patients and policymakers. DCCHs include community hospitals, which treat various other medical conditions aside from cancer, larger university teaching hospitals and high-volume cancer research centers. The roles of these hospitals are not clearly defined and may even overlap in many cases. Due to the lack of descriptive statistics, important policy questions remain unanswered. Should large university hospitals and cancer centers with high cancer patient volume focus their care on relatively younger patients who tend to have fewer medical complications and are more likely to be eligible for clinical trials? Or should they instead treat more complicated cases, such as patients with multiple comorbidities or frail elderly patients who may need multidisciplinary care? Some evidence suggests that older cancer patients benefit greatly by being treated at

high-volume hospitals because these patients are at high risk of death (20). Although information in this study is insufficient to make conclusions about the complexity of cases being treated at high-volume hospitals, our study findings can be used to initiate future discussion among clinicians, patients and policymakers concerning how cancer care should be coordinated across various hospitals.

Finally, it is important to note that our findings may reflect patient preference. Currently, no formal referral structure exists for cancer patients in Japan. The Japanese health insurance system scheme grants patients unrestricted access to tertiary and specialized care, allowing patients to be seen for the first time at cancer centers and university hospitals, without referrals from their local practitioners (21). Aside from a small fee that hospitals can charge for a first patient visit without a referral, no restrictions are in place to stop patients from directly accessing specialists at high-volume hospitals. As younger and more mobile patients tend to choose hospitals more proactively than older patients or patients who have difficulty traveling (22), the lack of restriction allows younger and mobile elderly patients to seek care at high-volume hospitals that are far, even if they have low-volume hospitals nearby (23). Treatment-seeking behavior of cancer patients by stage is a topic that has not been investigated fully and will need to be addressed in future studies.

Our study has several limitations. First, our analyses only included data from DCCHs and may not be applicable to small community hospitals with different case-mix. However, we believe that our findings capture the majority of care practice patterns in Japan since the HBCR database covers ~70% of all cancer incidence (13). Second, our analysis is limited to five cancer types and should not be generalized to other cancers that are less common.

In conclusion, higher-volume designated cancer care hospitals in Japan tend to have a higher proportion of earlier-stage cancer patients for gastric, breast, colorectal, non-small cell lung and liver cancers. Moreover, higher-volume hospitals have a lower proportion of patients aged >75 years for these five cancer types. Our findings reinforce the importance of not making hospital performance comparisons in volume–outcome relationships using simple statistical adjustments. We hope that findings from this study are used to ignite further discussions among policymakers and various stakeholders on patient referral systems, and serve as one piece of evidence to help assign appropriate roles and resources to cancer treatment hospitals in Japan.

Funding

This project was funded as a grant-in-aid by National Cancer Center, Japan, grant number 25-A-21.

Conflict of interest statement

None declared.

References

1. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001;345:181–8.
2. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–37.
3. Vrijens F, Stordeur S, Beirens K, Devriese S, Van Eycken E, Vlayen J. Effect of hospital volume on processes of care and 5-year survival after breast cancer: a population-based study on 25000 women. *Breast* 2012;21:261–6.
4. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011;364:2128–37.
5. Huo J, Lairson DR, Du XL, et al. Hospital case volume is associated with improved survival for patients with metastatic melanoma [published online ahead of print April 21 2014]. *Am J Clin Oncol* 2014. doi: 10.1097/COC.0000000000000074.
6. Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. *Cochrane Database Syst Rev* 2012;3:CD005391.
7. Iezzoni LI. *Risk Adjustment for Measuring Health Care Outcomes*. 4th edn. Chicago: Health Administration Press, 2012.
8. Iezzoni LI. Using risk-adjusted outcomes to assess clinical practice: an overview of issues pertaining to risk adjustment. *Ann Thorac Surg* 1994;58:1822–6.
9. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of hospital procedure volume on ovarian cancer survival in Japan, a country with low incidence of ovarian cancer. *Cancer Sci* 2004;95:233–7.
10. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of hospital procedure volume on uterine cancer survival in Osaka, Japan. *Cancer Sci* 2005;96:689–94.
11. Nomura E, Tsukuma H, Ajiki W, Ishikawa O, Oshima A. Population-based study of the relationship between hospital surgical volume and 10-year survival of breast cancer patients in Osaka, Japan. *Cancer Sci* 2006;97:618–22.
12. Ichikawa D, Komatsu S, Kubota T, et al. Effect of hospital volume on long-term outcomes of laparoscopic gastrectomy for clinical stage I gastric cancer. *Anticancer Res* 2013;33:5165–70.
13. Higashi T, Nakamura F, Shibata A, Emori Y, Nishimoto H. The national database of hospital-based cancer registries: a nationwide infrastructure to support evidence-based cancer care and cancer control policy in Japan. *Jpn J Clin Oncol* 2014;44:2–8.
14. Liver Cancer Study Group of Japan. *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer*. 5th edn, revised version. Tokyo: Kanehara & Co. Ltd., 2009.
15. Jensen LS, Nielsen H, Mortensen PB, Pilegaard HK, Johnsen SP. Enforcing centralization for gastric cancer in Denmark. *Eur J Surg Oncol* 2010;36 (Suppl 1):S50–4.
16. Dikken JL, Dassen AE, Lemmens VE, et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. *Eur J Cancer* 2012;48:1004–13.
17. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg* 1998;228:429–38.
18. Braga LH, Farrokhyar F, Bhandari M. Confounding: what is it and how do we deal with it? *Can J Surg* 2012;55:132–8.
19. Zhang W, Ayanian JZ, Zaslavsky AM. Patient characteristics and hospital quality for colorectal cancer surgery. *Int J Qual Health Care* 2007;19:11–20.
20. Dimick JB, Cowan JA Jr., Upchurch GR Jr., Colletti LM. Hospital volume and surgical outcomes for elderly patients with colorectal cancer in the United States. *J Surg Res* 2003;114:50–6.
21. Ikegami N, Yoo BK, Hashimoto H, et al. Japanese universal health coverage: evolution, achievements, and challenges. *Lancet* 2011;378:1106–15.
22. Victoor A, Delnoij DM, Friele RD, Rademakers JJ. Determinants of patient choice of healthcare providers: a scoping review. *BMC Health Serv Res* 2012;12:272.
23. Stitzenberg KB, Sigurdson ER, Egleston BL, Starkey RB, Meropol NJ. Centralization of cancer surgery: implications for patient access to optimal care. *J Clin Oncol* 2009;27:4671–8.

Journal of Radiation Research Advance Access published April 24, 2015

Journal of Radiation Research, 2015, pp. 1–7
doi: 10.1093/jrr/rrv027
Regular Paper

Current status and outcomes of patients developing PSA recurrence after prostatectomy who were treated with salvage radiotherapy: a JROSG surveillance study

Takashi Mizowaki[1]*, Manabu Aoki[2], Katsumasa Nakamura[3], Atsunori Yorozu[4], Masaki Kokubo[5], Katsuyuki Karasawa[6], Takuyo Kozuka[7], Nobuaki Nakajima[8], Keisuke Sasai[9] and Tetsuo Akimoto[10]

[1]Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan
[2]Department of Radiology, The Jikei University School of Medicine, 3-25-8 Nishishinbashi, Minato-ku, Tokyo, 105-8461, Japan
[3]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Umade, Higashi-ku, Fukuoka, 812-8582, Japan
[4]Department of Radiology, National Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo, 152-8902, Japan
[5]Department of Radiation Oncology, Kobe City Medical Center General Hospital, 2-1-1 Minatojimaminamimachi, Chuo-ku, Kobe, 650-0047, Japan
[6]Department of Radiology, Tokyo Metropolitan Cancer and Infectious diseases Center, Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo, 113-8677, Japan
[7]Department of Radiation Oncology, Cancer Institute Hospital, 3-8-31 Ariake, Kouto-ku, Tokyo, 135-8550, Japan
[8]Department of Radiology, Shizuoka General Hospital, 4-27-1 Kitaando, Aoi-ku, Shizuoka, 420-8527, Japan
[9]Department of Radiology, Juntendo University School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo, 113-8431, Japan
[10]Department of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa City, Chiba, 277-8577, Japan
*Corresponding author. Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University. 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507 Japan. Tel: +81-75-751-3419; Fax: +81-75-751-3422; Email: mizo@kuhp.kyoto-u.ac.jp
Received December 22, 2014; Revised February 15, 2015; Accepted March 20, 2015

ABSTRACT

The conditions and outcomes of Japanese patients with prostate cancer who developed PSA failure after radical prostatectomy (RP), and who were treated via salvage radiotherapy (S-RT), were surveyed. Clinical data on S-RT were gathered in questionnaires completed by facilities participating in the Japanese Radiation Oncology Study Group. S-RT was defined as external-beam radiotherapy delivered to the prostate beds of patients with prostate cancer who had eventually developed PSA failure, although their PSA values had at one stage attained levels <0.2 ng/ml following RP. Hormonal therapy was combined with S-RT in ~40% of cases. Outcomes were evaluated in 186 cases treated via S-RT alone. The nadir PSA level after RP, and the level upon initiation of S-RT, were 0.0135 ng/ml and 0.292 ng/ml, respectively. The median period between RP and S-RT was 18.6 months. The median follow-up period was 58 months. The 5-year PSA recurrence–free survival (PRFS) and clinical failure–free survival (CFFS) rates were 50.1% (95% CI: 42.8–57.9%) and 90.1% (95% CI: 86.4–95.7%), respectively. PRFS was significantly superior in patients with PSA values ≤0.3 ng/ml upon initiation of S-RT than in those with PSA values >0.3 ng/ml (57.5% vs 40.5%, $P = 0.027$). In Japan, hormonal therapy is combined with S-RT in ~40% of cases. The 5-year PRFS and CFFS rates of cases treated via S-RT alone were 50.1% and 90.1%, respectively. A PSA value of 0.3 ng/ml served as a significant cut-off for prediction of PRFS.

KEYWORDS: salvage radiotherapy, prostate cancer, PSA recurrence, radical prostatectomy

INTRODUCTION

Radical prostatectomy (RP) is one of the principal treatment modalities for localized prostate cancer. However, about 20–30% of patients with localized disease treated via RP eventually experience recurrences [1]. Of such cases, some patients exhibit clinical recurrence, including lymph node and bone metastases. However, most recurrences are prostate-specific antigen (PSA) recurrences, in which continuous rises in PSA levels are observed, without any evidence of clinical failure, after a very low PSA nadir value has been attained after RP. It has been reported that 34% of PSA-recurrent cases develop metastatic disease at a median time of 8 years after such PSA elevations, and die at a median time of 5 years from development of metastatic disease [1].

In patients exhibiting PSA recurrence, salvage radiotherapy (S-RT) is considered to be the only curative treatment. Therefore, S-RT has been widely used to treat those who have developed PSA recurrence after RP, although the impact thereof on survival remains under investigation by the Japan Clinical Oncology Group (JCOG) (the JCOG 0401 study [2]). The American Society for Radiation Oncology (ASTRO)/American Urological Association (AUA) guidelines strongly recommend that S-RT should be offered to patients exhibiting PSA or local recurrence after RP, if there is no evidence of distant metastatic disease [3]. However, no nationwide data on the outcomes of S-RT in Japan are available. Therefore, we conducted the present study to determine the actual conditions and outcomes of patients treated with S-RT upon the development of PSA recurrence after RP in Japan.

METHODS

A registry was established by facilities participating in the Japanese Radiation Oncology Study Group (JROSG). Eligible cases were patients with localized prostate cancer who were treated via RP prior to 2005 and who received S-RT between January 2005 and December 2007 because of PSA failure. The cut-off PSA value for PSA failure was defined as 0.2 ng/ml based on the Guidelines for Clinical Practices of Prostate Cancer edited by the Japanese Urorogical Association [4], and the ASTRO/AUA guidelines [3]. S-RT featured external-beam radiotherapy delivered to the prostate beds of patients with prostate cancer who had eventually developed PSA failure after RP, although their PSA levels had once dropped below 0.2 ng/ml at some point after RP. Therefore, patients with minimum PSA values after RP (the PSA nadirs) of 0.2 ng/ml or higher were excluded from the present study. In addition, the interval between RP and S-RT was essentially required to be 6 months or longer. Patients in whom EBRT was delivered to the prostate bed earlier than 3 months after RP were considered to have received adjuvant radiotherapy, and their data were reported separately [5]. Because pre-operative and operative factors have been well studied [6, 7], this survey focused on the post-operative factors relating to S-RT in order to maximize the reliability of data from busy JROSG facilities.

PSA recurrence–free survival (PRFS) and clinical failure–free survival (CFFS) rates were calculated via the Kaplan–Meier method, commencing on the dates of initiation of S-RT. The statistical significances of observed differences in survival curves were estimated using the log-rank test. PSA recurrence developing after S-RT was defined as follows: The PSA level became re-elevated to 0.2 ng/ml or higher in patients in whom the PSA level had once dropped below 0.2 ng/ml after S-RT, or was 0.2 ng/ml or higher on the date of the first measurement of PSA level after S-RT if the PSA level had never fallen below 0.2 ng/ml. Cox's proportional hazard modeling was used to explore the predictive significance of factors associated with PRFS. The grading of each adverse event was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0; JCOG [8]. The Mann–Whitney U-test was used to compare the incidences of adverse events among patients treated with different radiation techniques or radiation doses. Statistical analyses were performed with the aid of GraphPad Prism 5.04 (GraphPad Software Inc., La Jolla, CA, USA) and StatView (ver. 5.0; SAS Institute Inc., Cary, NC, USA) software packages.

The present study was designed and conducted by the Urologic Oncology Subgroup of the JROSG. The study was also approved by the Institutional Review Boards of Kyoto University (Approval No.: E-1007) and Jikei University, and conducted in accordance with the dictates of the Helsinki Declaration.

RESULTS

Overview of the cases

Data on 371 cases treated in 38 facilities were sent to the JROSG registry between October 2011 and January 2012. Hormonal therapy was combined with S-RT in 151 patients (40.7% of all cases). In three cases, chemotherapy was added before or after S-RT. The rest of the cases were treated via S-RT alone. However, prognostic information was insufficient in 28 cases, and the PSA nadir value was higher than 0.2 ng/ml in a further 3 cases. Therefore, PRFS and CFFS were evaluated for the remaining 186 cases who met the criteria for S-RT and who were treated via S-RT alone. PSA doubling time was not included in the current analyses, because it was not reported in many cases.

Characteristics of cases treated via S-RT alone

The characteristics of the 186 cases treated via S-RT alone are summarized in Table 1. The median patient age was 67 years. The nadir

Table 1. Characteristics of the S-RT–alone cases

Age (years)	Range: 49–82
	Median: 67
	Mean: 66
PSA nadir after RP (ng/ml)	Range: <0.0–0.191
	Median: 0.0135
	Mean: 0.032
PSA at initiation of S-RT (ng/ml)	Range: 0.02–3.63
	Median: 0.292
	Mean: 0.402
Period between RP and initiation of S-RT (months)	Range: 3.8–80.5
	Median: 18.6
	Mean: 24

PSA = prostate-specific antigen, RP = radical prostatectomy, S-RT = salvage radiotherapy.

Table 2. Summary of salvage radiotherapies

Treatment planning method		Number of cases
	CT-based plan	155
	X-ray simulation	31
Irradiated area		
	Prostate bed	176
	Small pelvis	8
	Whole pelvis	2
Radiation technique		
	Five or more fields	88
	Four fields	96
	Other	2
Total dose		
	>70 Gy	6
	>65 Gy to ≤70 Gy	70
	>60 Gy to ≤65 Gy	105
	≤ 60 Gy	5

CT = computed tomography.

PSA level after RP and the PSA level at initiation of S-RT were 0.0135 ng/ml and 0.292 ng/ml, respectively. The median period between RP and S-RT was 18.6 (range: 3.8–80.5) months. In seven cases, S-RT was commenced between 3 and 6 months after RP (3.8–5.2 months).

Details of S-RT

Of the 186 cases, computed tomography-based simulations were performed on 155, whereas X-ray simulations were performed on 31. The prostate bed, small pelvis and entire pelvis were irradiated in 176, 8 and 2 cases, respectively. Three-dimensional conformal radiation therapy (3D-CRT) with five portals or more, the four-field box technique, and an anterior–posterior opposing field, were used in 88, 96 and 2 cases, respectively. The X-ray energies were as follows: 6 MV in 6, 10 MV in 144, and >10 MV in 34 cases, respectively. The prescribed doses were >70 Gy, >65 Gy to ≤70 Gy, >60 Gy to ≤65 Gy, and ≤60 Gy in 6, 70, 105 and 5 patients, respectively. The cone-down technique was used in 71 cases, with boost plans applied after a median dose of 45.8 Gy (range: 30–60 Gy) had been delivered. A summary of the S-RTs applied is shown in Table 2.

Oncological outcomes of S-RT

The median follow-up period was 58 months (range: 3–83 months). The 5-year PRFS and CFFS were 50.1% (95% CI: 42.8–57.9%) and 90.1% (95% CI: 86.4–95.7%), respectively (Figs 1 and 2). Of the PSA level at initiation of S-RT (the pre-S-RT PSA), the PSA nadir attained after RP, the period between RP and S-RT, radiation dose, and age, only the pre-S-RT PSA level significantly predicted PRFS upon both univariate and multivariate analyses (Table 3). The PRFS was significantly longer in patients with PSA values ≤0.3 ng/ml at initiation of S-RT than in those with PSA levels >0.3 ng/ml (57.5% vs 40.5%, $P = 0.027$) (Fig. 3). With other PSA cut-off values at S-RT, the differences were not statistically significant ($P = 0.44$, 0.051 and 0.21 for 0.2, 0.4 and 0.5 ng/ml, respectively).

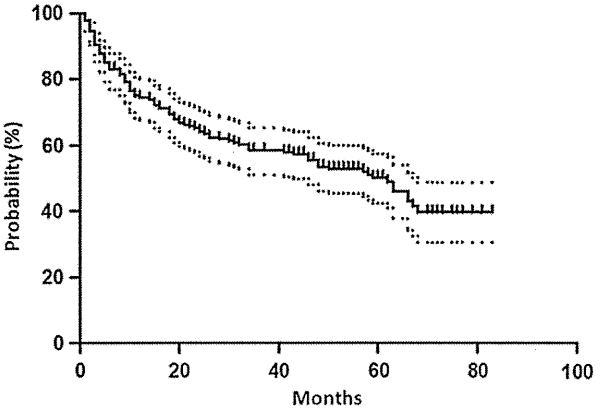

Fig 1. Kaplan–Meier curve with 95% confidence interval of PSA recurrence–free survival.

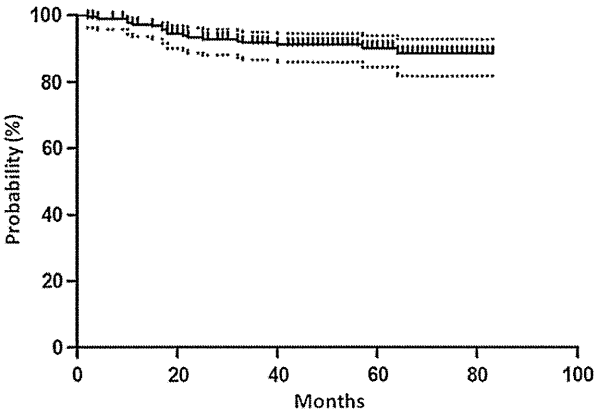

Fig 2. Kaplan–Meier curve with 95% confidence interval for clinical failure–free survival.

Adverse events

The crude incidences of Grade 1, 2 and 3 acute adverse events were 51.1%, 7.0% and 0.5% for genitourinary (GU) events, and 36.6%, 22.0% and 0% for gastrointestinal (GU) events, respectively. No Grade 4 or higher acute adverse event was observed. The acute toxicities are listed in Table 4. Reported late adverse events are summarized in Table 5. The crude incidences of Grade 1, 2 and 3 late adverse events were 29.6%, 13.4% and 2.7% for GU events, and 15.6%, 4.3% and 0% for GI events, respectively. No Grade 4 or higher late toxicity was observed in either the acute or late phase.

Incidences of acute GU, acute GI and late GI adverse events were significantly lower in patients treated with ≥5-field technique

Table 3. Univariate and multivariate analyses of factors predicting PSA failure–free survival upon Cox's proportional hazard modeling

	Univariate			Multivariate		
Factor	HR	95% CI	*P*	HR	95% CI	*P*
Pre-S-RT PSA	1.60	(1.01–2.52)	0.045	1.64	(1.03–2.61)	0.035
PSA nadir after RP	1.61	(0.01–259.95)	0.85	0.375	(0.002–88.09)	0.73
Period between RP and S-RT	1.00	(1.00–1.00)	0.68	1.00	(1.00–1.00)	0.28
Radiation dose (<65 Gy)	1.41	(0.92–2.15)	0.12	1.44	(0.94–2.22)	0.096
Age	1.02	(0.98–1.05)	0.31	1.02	(0.99–1.06)	0.24

PSA = prostate-specific antigen, S-RT = salvage radiation therapy, RP = radical prostatectomy, HR = hazard ratio, CI = confidence interval.

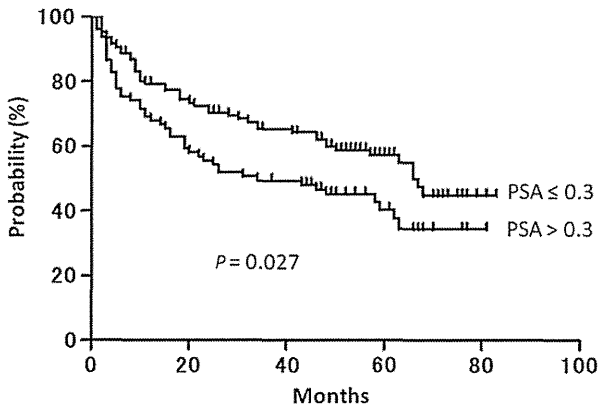

Fig 3. Kaplan–Meier curves for PSA recurrence–free survival, according to PSA level at initiation of salvage radiotherapy (PSA ≤ 0.3 ng/ml vs PSA > 0.3 ng/ml).

compared with those who irradiated with the 4-field technique (*P* value: <0.0001, 0.0063 and 0.0024, respectively) (Tables 6 and 7). On the other hand, incidences of late GU events were significantly higher in patients who received higher radiation doses ($P = 0.028$) (Table 7).

DISCUSSION

S-RT is recognized as the sole approach affording an opportunity of a cure to patients with localized prostate cancer who develop PSA recurrence after RP [6]. The principal purpose of S-RT is to reduce the PSA level to the limit of detection, and maintain PSA recurrence-free status. According to a recent publication, the PSA recurrence-free rates were generally 30–60% 3–6 years after S-RT [6]. King performed a systematic review of S-RT based on the data of 41 reports, including 5597 cases, and the average 5-year PSA control rate was 46.2% [9]. In Japan, Kinoshita reported a 5-year PSA recurrence–free rate of 42.2% [10]. Therefore, long-term PSA control can generally be expected in about half of all patients who receive S-RT. The result of a current surveillance study (5-year PRFS rate = 50.4%) is very consistent with those of previous reports, and it will be possible to conclude that long-term PSA control may be expected in about half of all patients treated with S-RT, in Japan, following PSA failure after RP.

Various predictors of PRFS have been reported, including the pathological T-stage at RP, seminal vesicle (SV) invasion, surgical margin status, Gleason's score (GS), the period elapsing between RP and PSA failure, combined hormonal therapy, PSA doubling time, radiation dose, and PSA level at the time of S-RT initiation (pre-S-RT PSA) [6]. Generally, higher T-stage, positive SV invasion, a higher GS, a shorter period between RP and PSA failure, a shorter PSA doubling time, a lower radiation dose, and a higher pre-S-RT PSA level, predict poor PRFS. However, considerable among-report inconsistencies are evident.

Among possible predictors of PRFS, the pre-S-RT PSA level has consistently been found to be significant. King, in a comprehensive systematic review of S-RT, found that only the pre-S-RT PSA level ($P < 0.001$) and the radiation dose ($P = 0.052$) were independent significant predictors of PRFS [6, 9]. The PFRS fell by an average of 2.6% for each incremental 0.1 ng/ml of PSA level at the time of initiation of S-RT. This study affords Level 2a evidence for initiation of S-RT at the lowest possible PSA level. The results of our current study are in line with those of King. In the present study, the 5-year PRFS rates were 57.5% and 40.5% for patients who received S-RT at PSA values of 0.3 ng/ml or lower, and those commenced on S-RT at PSA levels over 0.3 ng/ml, respectively ($P = 0.027$).

We believe this finding is very important, because it finds immediate application in daily clinical practice. It is not in fact difficult to commence S-RT in routine practice as early as possible after PSA failure is observed, to (possibly) improve PRFS. In this sense, the pre-SRT PSA level is a very practicable predictive factor that can be used in daily clinical practice. On the other hand, most other possible predictive factors, including pathological T-stage, SV invasion, surgical margin status, and GS, are based on pre-operative or operative data. If a patient develops PSA failure after RP, it is usually difficult to decide not to offer S-RT to those with unfavorable predictions, because S-RT is the sole definitive treatment for cases who develop PSA recurrence after RP, and not all patients with poor predictors fail to benefit from S-RT.

Another possible means of improving PRFS after S-RT may be dose escalation. In the work of King, radiation dose was another independent predictor of PRFS [9]. S-RT doses in the range 60–70 Gy lie in the steep region of the sigmoid dose–response curve; a dose of 70 Gy was associated with 54% PRFS compared with only 34% for 60 Gy. However, no consensus has yet been reached on the optimal

Table 4. Incidences of acute adverse events

		Incidence (%)				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GU	Miction pain	82.3	17.7	0	0	0
toxicity	Incontinence	87.6	11.3	1.1	0	0
	Pollakisuria/urgency	48.4	45.7	5.9	0	0
	Retention/obstruction	91.4	8.1	0	0.5	0
	Any GU event	41.4	51.1	7.0	0.5	0
GI	Proctitis	70.4	29.0	0.5	0	0
toxicity	Rectal bleeding	80.1	15.6	4.3	0	0
	Perianal mucositis	58.6	21.5	19.9	0	0
	Any GI event	41.4	36.6	22.0	0	0

GU = genitourinary, GI = gastrointestinal.

Table 5. Incidences of late adverse events

		Incidence (%)				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GU	Miction pain	93.0	7.0	0	0	0
toxicity	Incontinence	68.8	23.1	7.5	0.5	0
	Pollakisuria/ urgency	80.6	17.2	2.2	0	0
	Retention/ obstruction	91.4	5.9	1.6	1.1	0
	Hematuria	82.3	12.9	3.8	1.1	0
	Any GU event	54.3	29.6	13.4	2.7	0
GI	Proctitis	90.3	9.1	0.5	0	0
toxicity	Rectal bleeding	83.3	15.1	1.6	0	0
	Perianal mucositis	91.4	5.9	2.7	0	0
	Any GI event	80.1	15.6	4.3	0	0

GU = genitourinary, GI = gastrointestinal.

radiation dose for S-RT. In the present work, the radiation dose did not predict PRFS. This may be attributable to the fact that most patients (94%) in our series were treated with doses of 60–70 Gy; only six cases (3%) received 70 Gy or higher. The impact of dose escalation during S-RT delivered in Japan should be explored in future.

Toxicities associated with S-RT were very limited in our series of patients, in agreement with previously published data [6]. In our series, no Grade 4 or higher acute or late toxicity (either GU or GI) was observed. The incidences of Grade 3 toxicities were only 0.5% and 0% (acute GU and GI toxicities) and 2.7% and 0% (late GU and GI toxicities), respectively.

Adjuvant radiotherapy (A-RT) is also strongly recommended to patients with adverse pathological findings after RP (i.e. SV invasion, positive surgical margins, and/or extracapsular extensions), based on three randomized trials, all of which found that A-RT was useful [3, 11–14]. No completed trial has directly compared S-RT with A-RT. Although several retrospective comparisons between the two approaches have been conducted, it is impossible to retrospectively determine whether either modality is superior to the other. This is

Table 6. Incidences of acute adverse events by radiation technique and total dose

		Incidence (%)					*P* value
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
Incidences of any acute GU events (%)	4 fields	24.0	64.6	10.4	1.0	0	**<0.0001**
	≥5 fields	60.2	37.5	2.3	0	0	
	≤65 Gy	43.6	50.0	5.5	0.9	0	0.44
	>65 Gy	38.2	53.9	7.9	0	0	
Incidences of any acute GI events (%)	4 fields	30.2	42.7	27.1	0	0	**0.0063**
	≥5 fields	52.3	30.7	17.0	0	0	
	≤65 Gy	44.5	35.5	20.0	0	0	0.27
	>65 Gy	36.8	38.2	25.0	0	0	

GU = genitourinary, GI = gastrointestinal.

Table 7. Incidences of late adverse events by radiation technique and total dose

		Incidence (%)					*P* value
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
Incidences of any late GU events (%)	4 fields	46.9	40.6	10.4	2.1	0	0.32
	≥5 fields	61.4	18.2	17.0	3.4	0	
	≤65 Gy	60.9	26.4	10.0	2.7	0	**0.028**
	>65 Gy	44.8	34.2	18.4	2.6	0	
Incidences of any late GI events (%)	4 fields	71.9	21.9	6.2	0	0	**0.0024**
	≥5 fields	89.8	8.0	2.2	0	0	
	≤65 Gy	80.0	15.5	4.5	0	0	0.95
	>65 Gy	80.3	15.8	3.9	0	0	

GU = genitourinary, GI = gastrointestinal.

because patients who would not have developed recurrences without further intervention were included in the A-RT group, whereas all patients receiving S-RT had actually suffered recurrences. Currently, two prospective randomized trials comparing A-RT with a 'wait-and-see' policy following S-RT initiation at early trigger points (PSA > 0.1 or 0.2 ng/ml) are ongoing [15, 16].

Although S-RT affords an ~50% chance of further long-term PSA control in patients who exhibit PSA recurrence after RP, no extra survival benefit thereof has been proven in comparison with hormonal therapy (HT) alone. The JCOG 0401 study was designed to answer this question [2]; however, the study is not yet complete. Even if the survival outcomes of the S-RT- and HT-alone groups are shown to be comparable, S-RT would still have the advantage of affording an HT-free chance in about half of all patients experiencing recurrence. Therefore, we believe that S-RT will play a useful role in patients who develop PSA failure after RP.

In conclusion, hormonal therapy is combined with S-RT in ~40% of cases in Japan. S-RT is commenced when the PSA level attains ~0.3 ng/ml (on average). The 5-year PRFS and CFFS rates of cases treated via S-RT alone were 50.1% and 90.1%, respectively. Incidences of acute GU, acute GI and late GI events were significantly lower in patients treated with 3D-CRT with five portals or more, when compared with those treated with the 4-field technique. A PSA value of 0.3 ng/ml was a significant cut-off predicting PRFS.

ACKNOWLEDGEMENTS

This study was a research project of the JROSG in 2012–2013. We thank all members of the JROSG Working Subgroup on Urologic Oncology and the JROSG office for support in the planning and execution of the study. We also appreciate the support provided by all institutions and researchers involved. The results of this study have been published, in part, as an abstract of the 2013 Genitourinary Cancers Symposium held 14–16 February 2013 in Orlando, FL, USA.

FUNDING

This work was partly supported by the Japanese Radiation Oncology Study Group (JROSG). Funding to pay the Open Access publication charges for this article was provided by the grants and endowments of Kyoto University (#200040700171).

REFERENCES

1. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *Jama* 1999;281:1591–7.
2. Yokomizo A, Kawamoto H, Nihei K, et al. Randomized controlled trial to evaluate radiotherapy +/- endocrine therapy versus endocrine therapy alone for PSA failure after radical prostatectomy: