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Practical patterns for stereotactic body radiotherapy to hepatocellular carcinoma in Korea: a survey of the Korean Stereotactic Radiosurgery Group

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Abstract

Objective: To investigate practical patterns for stereotactic body radiotherapy to hepatocellular carcinoma in Korea.

Methods: In June 2013, the Korean Stereotactic Radiosurgery Group of the Korean Society for Radiation Oncology conducted a national patterns-of-care survey about stereotactic body radiotherapy to the liver lesion in hepatocellular carcinoma, consisting of 19 questions and 2 clinical scenarios.

Results: All 208 radiation oncologists (100%), who are regular members of Korean Society for Radiation Oncology, responded to this survey. Among these, 95 radiation oncologists were specialists for hepatology; 64 physicians did not use stereotactic body radiotherapy for hepatocellular carcinoma, and 31 physicians used stereotactic body radiotherapy. Most physicians (52%) performed stereotactic body radiotherapy to hepatocellular carcinoma in ≤5 cases per year. Physicians applied stereotactic body radiotherapy according to tumour size and baseline Child–Pugh class. All physicians agreed the use of stereotactic body radiotherapy to 2.8-cm hepatocellular carcinoma with Child–Pugh class of A, while 23 physicians (74%) selected stereotactic body radiotherapy for Child–Pugh class of B. Nineteen physicians (61%) selected stereotactic body radiotherapy to 5-cm hepatocellular carcinoma with Child–Pugh class of A, and only 14 physicians (45%) selected stereotactic body radiotherapy for Child–Pugh class of B. On the other hand, the preferred dose scheme was same as 60 Gy in three fractions.

Conclusions: Among radiation oncologists in Korea, there was diversity in the practice for stereotactic body radiotherapy to the liver lesion in hepatocellular carcinoma. Additional prospective studies are necessary to standardize the practice and establish Korea-specific practice guidelines for hepatocellular carcinoma stereotactic body radiotherapy.

Key words: hepatocellular carcinoma, Korea, stereotactic body radiotherapy, survey

Introduction

Since stereotactic radiosurgery (SRS) was developed for the treatment of intracranial malignancies, stereotactic body radiotherapy (SBRT) was derived from SRS for the treatment of extracranial malignancies. Blomgren et al. (1) reported the first clinical use of SBRT to liver lesions in patients with hepatocellular carcinoma (HCC) at the Karolinska Institute in Stockholm in 1995. Since then, several prospective and retrospective studies on liver SBRT in HCC patients have reported a promising local control rate (LCR) and low risk of severe toxicity (2–5). Now, SBRT is considered as the alternative treatment option for HCC that is inoperable or unsuitable for other local treatments, and the National Comprehensive Cancer Network guidelines and the practice guidelines from Korean Liver Cancer Study Group and National Cancer Center recommend SBRT as a local treatment modality for the management of HCC (6,7).

Despite increased use of SBRT for HCC, current patterns of practice are unknown. Considering the vast heterogeneity in the management of HCC and some differences in equipment availability for SBRT, a wide variation in patterns of practice is expected (8). Recently, we conducted a nationwide survey on the use of SBRT in Korea and reported a continuous increase in its use, as well as a variety of practices surrounding its use (9). Therefore, the Korean Stereotactic Radiosurgery Group of the Korean Society for Radiation Oncology (KOSRO) conducted a national patterns-of-care survey to better understand practical patterns of SBRT for HCC in Korea.

Patients and methods

In Korea, SBRT for the treatment of extracranial malignancies is covered by the National Health Insurance Service when the number of fractions is 4 or fewer. Therefore, for this survey, we defined SBRT as radiotherapy with delivery of a high dose of radiation using ≤4 fractions to liver lesions in HCC patients. We sent the survey by e-mail to all 228 radiation oncologists, who are regular members of KOSRO, at 85 institutions in Korea in June 2013. A 19-questionnaire survey was designed to identify a specialist for hepatology and to determine practices surrounding the use of SBRT, including prescribed dose, moving organ control system, treatment machine and planning system. The full contents of the survey are available in Supplementary material 1. If the respondents were not a specialist for hepatology, they ended the survey on the first question and returned it by e-mail. If the respondents were specialist for hepatology, they were asked to complete the rest of the survey. Because they were able to select multiple answers to certain questions, the total percentage was >100% for selected questions. After 3 months, at which time we had collected the completed surveys by e-mail, we sent an additional survey including two clinical scenarios to only SBRT users: 2.8-cm HCC and 5-cm HCC. In this clinical setting, they selected SBRT or other fractionation schemes on their own judgement. The full contents of the survey are available in Supplementary material 2.The completed survey was returned by e-mail within 1 month. In the event of non-response, we contacted by telephone and sent e-mails in order to achieve a 100% response rate. This study was conducted under the authorization and cooperation of the Korea Radiation Oncology Group (KROG 13-14).

Results

The use of SBRT

In June 2013, 228 radiation oncologists were registered as regular members of KOSRO. Among these, 20 radiation oncologists were not involved in clinical practice owing to active service in the military, a temporary layoff or work as a general practitioner in primary health care. The remaining 208 KOSRO members actively participated in clinical practice, and all (100%) responded to the survey by August 2013. Among these, 95 KOSRO members responded that they acted as a specialist for hepatology. Of these, 31 physicians (33%) from 27 institutions used SBRT to treat liver lesions in HCC patients. The most common reason for the use of SBRT was the delivery of a higher dose than that possible with conventional radiotherapy (68%), followed by the shortening of treatment duration in order to start another treatment as early as possible (23%). Additional reasons were the shortening of treatment duration to improve patients' convenience and to reduce the mechanical load of the treatment machine (6%), and participation in a clinical trial (3%). When the respondents were allowed up to two answers, the most common reason for not using SBRT was the lack of appropriate patients for SBRT (56%), followed by the lack of special equipment (34%), and the use of other fractions such as hypofractionation or conventional fractionation (28%). Additional reasons were adoption of other treatment modalities (8%), the lack of experience with use of SBRT (6%), the existence of another SBRT expert (5%) and preparation for use of SBRT (3%).

In Korea, the number of physicians using SBRT has shown a gradual increase, since one physician applied SBRT to the liver lesion in HCC patients in 2003 (Fig. 1A). In 2013, the number of SBRT cases per physician per year was ≥50 in 2 physicians (7%), 40–50 in 1 (3%), 10–30 in 6 (19%), 6–10 in 6 (19%) and ≤5 in 16 (52%). When HCC patients were consulted to receive radiotherapy for the liver lesion, the application rate of SBRT was mostly <50% (Fig. 1B). Only two physicians who work at the same institution responded with an application rate of ≥90%. The most commonly prescribed doses for SBRT varied among physicians, as shown in Fig. 2A. The most common scheme was 60 Gy in three fractions (26%), followed by 45 Gy in three fractions (16%). When physicians adopted liver dose constraints, the normal liver volume [the total liver volume minus the planning target volume (PTV)] was considered as the significant liver volume by 28 physicians (90%), and the total liver volume by 3 physicians (10%). Reference points of liver dose constraints varied, as shown in Fig. 2B; $V_{15\ Gy}$ (at least 700 ml of the normal liver volume had to receive a total dose of <15 Gy, 29%), $V_{17\ Gy}$ (at least 700 ml of the normal liver volume had to receive a total dose of <17 Gy, 26%) and the mean dose (16%) were the most common liver dose constraints.

The preferred method of planning computed tomography (CT) for SBRT was four-dimensional CT (20 physicians, 65%), followed by inhalation and exhalation-breath-hold CT (19%), free-breathing CT combined with fluoroscopy (10%) and free-breathing CT (6%). The preferred method of immobilization during planning CT was alpha cradle/vacuum-lock, followed by a combination of stereotactic body frame plus alpha cradle/vacuum-lock plus wingboard. For control of liver motion, respiratory-gated radiotherapy with Real-Time Position Management (Varian Medical Systems, Palo Alto, CA) was preferred. Details of the preferred methods are summarized in Table 1. Various treatment machines were available for liver SBRT: nine physicians (29%) applied two or more specially equipped treatment machines and could select the most suitable treatment machine on a case-by-case basis. The most commonly used treatment machines were RapidArc (Varian Medical Systems) and CyberKnife (Accuray Inc., Sunnyvale, CA). Details of the treatment machines are summarized in Table 2. For SBRT planning, nine physicians (29%) used two planning systems. The majority (65%) used Eclipse (Varian Medical Systems). In addition, 29% of the physicians used the CyberKnife planning system,

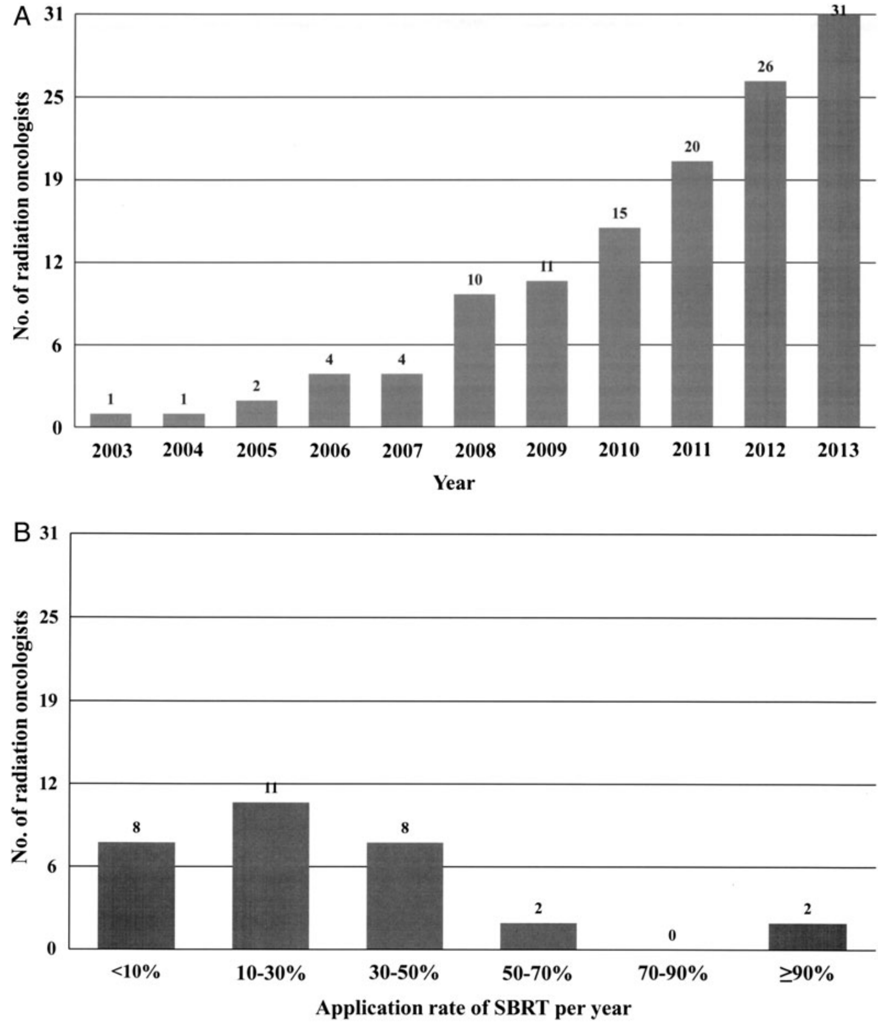

Figure 1. (A) Cumulative adoption of stereotactic body radiotherapy (SBRT) to the liver lesion in hepatocellular carcinoma (HCC) after its introduction in 2003. (B) Application rate of liver SBRT per physician per year in HCC patients.

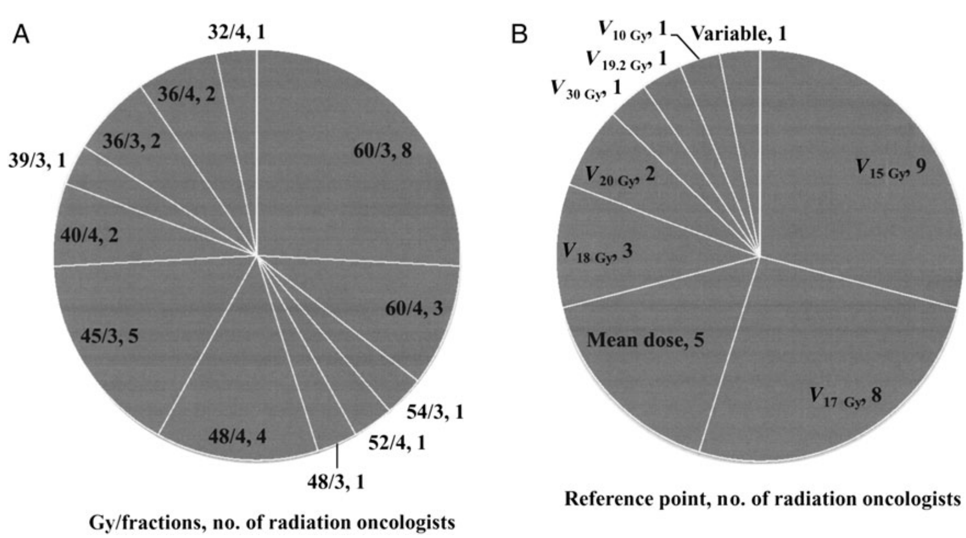

Figure 2. (A) The most commonly prescribed doses for SBRT to the liver lesion in HCC. (B) Reference points of liver dose constraints for liver SBRT in HCC: $V_{x\ \mathrm{Gy}}$ means the normal liver volume receiving <X Gy; variable means that the radiation oncologist selected the reference points case by case.

Table 1. Details of the preferred methods for immobilization and control of liver motion for stereotactic body radiotherapy to hepatocellular carcinoma in Korea

Methods of immobilization	No. of radiation oncologists (%)
Alpha cradle/vacuum-lock	9 (29)
Alpha cradle/vacuum-lock + wingboard	5 (16)
Stereotactic body frame	2 (7)
Stereotactic body frame + alpha cradle/ vacuum-lock	1 (3)
Stereotactic body frame + alpha cradle/ vacuum-lock + wingboard	6 (19)
Wingboard	4 (13)
No use	4 (13)
Methods of liver motion control	**No. of radiation oncologists (%)**
Respiratory gating method: Varian RPM	15 (48)
Respiratory gating method: ExacTrac gating-Novalis gating	2 (7)
Forced shallow breathing with abdominal compression	10 (32)
Real-time tumour-tracking methods	2 (7)
No use	2 (6)

Table 2. Details of the treatment machines for stereotactic body radiotherapy to hepatocellular carcinoma in Korea

Types of treatment machines	No. of radiation oncologists[a] (%)
RapidArc_Varian	10 (32)
CyberKnife	9 (29)
Clinac iX_Varian	6 (19)
Novalis_Varian	6 (19)
TrueBeam_Varian	4 (13)
Tomotherapy	3 (10)
VMAT_Elekta	2 (7)
Novalis Tx_Varian	1 (3)

[a]To identify all available equipment, the respondents selected multiple answers.

16% used the iPlan (BrainLAB AG, Feldkirchen, Germany), 7% used the Pinnacle system (Philips, Milpitas, CA) and 7% used MONACO (Electa, Crawley, UK). For optimal dose distribution for the tumour and the liver, 18 physicians (58%) used multiple planning techniques. The most commonly applied planning techniques were static intensity-modulated radiotherapy (IMRT) (61%), followed by dynamic conformal arc radiotherapy (55%), three-dimensional conformal radiotherapy (3DCRT) with multiple beam arrangements (29%), robotic SBRT (29%) and rotational IMRT (10%).

To assist in target localization, fiducial insertion was always performed by three physicians (10%) and sometimes by eight physicians (26%). For target localization before each treatment, the preferred verification method was conebeam CT (74%), followed by orthogonal kilovoltage radiography (13%), orthogonal megavoltage radiography (10%) and fluoroscopy (3%). The application rate of gating treatment was 0% in 13 physicians (43%), <10% in 4 (13%), 10–40% in 2 (6%), 40–60% in 2 (6%), 60–90% in 2 (6%), ≥90% in 2 (6%) and 100% in 6 (20%). When patients received SBRT, 11 physicians (35%) delivered it on consecutive days; 18 physicians (58%), with 48-h intervals between fractions and 2 physicians (7%), with 72-h intervals between fractions. The overall treatment was ended within 1 week (55%) or 2 weeks (45%). At the time, 13 respondents (42%) were participating in clinical trials.

Clinical cases

The first case was a 49-year-old male patient with 2.8-cm HCC at the liver dome. The lesion was inoperable owing to an underlying medical problem and was unsuitable for radiofrequency ablation. He received one cycle of transarterial chemoembolization (TACE). The follow-up CT after TACE showed a viable tumour with incomplete lipiodol uptake (Fig. 3A), and he was consulted for radiotherapy. The normal liver volume was measured as 1359 ml on planning CT. If the baseline liver function was Child–Pugh (CP) class of A, all 31 physicians agreed on the use of SBRT (Fig. 3B). However, in case of CP class of B, 23 physicians (74%) selected SBRT (Fig. 3C), while 8 physicians (26%) selected altered fractionation schedules (6 physicians adopted hypofractionation and 2 physicians adopted conventional fractionation). The second case was a 57-year-old male patient with 5-cm HCC at the liver dome. He received three cycles of TACE. The follow-up CT after TACE showed a viable tumour with incomplete lipiodol uptake (Fig. 3D), and he was consulted for radiotherapy. The normal liver volume was measured as 1435 ml. In case of CP class of A, SBRT was chosen by 19 physicians (61%, Fig. 3E), hypofractionation by 10 (32%) and conventional fractionation by 2 (7%). In case of CP class of B, SBRT was chosen by only 14 physicians (45%, Fig. 3F), hypofractionation by 13 (42%) and conventional fractionation by 4 (13%). Although physicians selected SBRT according to tumour size and baseline liver function, the preferred dose scheme was 60 Gy in three fractions for all cases.

During the SBRT planning process, magnetic resonance imaging (MRI) to assist target delineation was always used by only three physicians and sometimes used by six physicians. The majority (71%) did not use MRI. The most commonly applied interval from completion of SBRT to the first follow-up imaging study was 4 weeks (65%), followed by 8 weeks (32%), and 12 weeks (3%). The preferred imaging techniques for surveillance were CT alone (42%) or a combination of CT and MRI (39%). Two physicians selected the type of follow-up image (CT or MRI) based on the pretreatment image. Some physicians preferred a combination of PET-CT and other techniques: CT (one physician) or MRI (one physician), or CT and MRI (two physicians).

Discussion

In Korea, practical patterns of radiotherapy to HCC have changed over time. The Korean Liver Cancer Study Group conducted the first national survey on radiotherapy for HCC patients in 2006 (10). Among 53 institutions that were running in Korea at that time, only 10 institutions (19%) treated at least 5 HCC patients with external beam radiotherapy between 2004 and 2005. Applied planning techniques were 3DCRT (82%), IMRT (1%), two-dimensional conventional radiotherapy (8%) and CyberKnife (9%). On the other hand, 27 institutions (32%) used SBRT to the liver lesion in HCC in 2013; 15 institutions (18%) treated at least 6 HCC patients with SBRT per year. However, the application rate of SBRT for HCC is still lower than that of other cancers, especially primary or metastatic lung cancers, considering that a previous national survey conducted by our group on the use of SBRT in Korea for the treatment of various tumours reported that 38 institutions (45%) have used SBRT (9). Our current survey that the application rate of SBRT to HCC was mostly <50%, and that

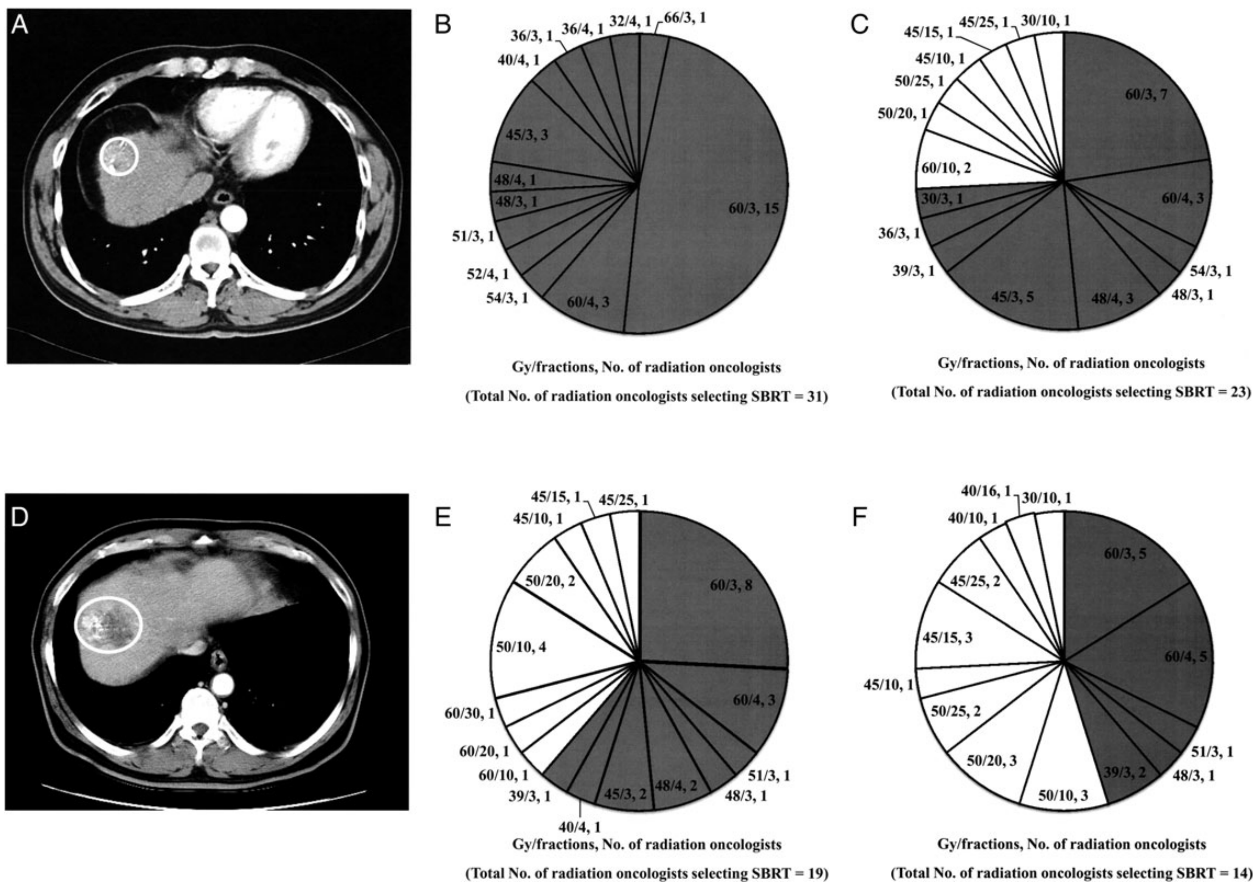

Figure 3. (A) A 49-year-old male patient with 2.8-cm HCC at the liver dome. Computed tomography (CT) after one cycle of transarterial chemoembolization (TACE) showed a viable tumour with incomplete lipiodol uptake (white circle). (B) SBRT doses if the baseline liver function was Child–Pugh (CP) class of A and radiation oncologist selected SBRT. (C) Selected fractionation schemes if the baseline liver function was CP class of B. (D) A 57-year-old male patient with 5-cm HCC at the liver dome. CT after three cycles of TACE showed a viable tumour with incomplete lipiodol uptake (white circle). (E) Selected fractionation schemes if the baseline liver function was CP class of A. (F) Selected fractionation schemes if the baseline liver function was CP class of B.

the main reason for not using SBRT to treat HCC was the lack of appropriate patients supported this.

Although there are some difference in organ control systems, treatment machines and planning systems, the greatest difference in practical patterns of SBRT for HCC lies in fractionation schemes. SBRT is defined as a 'newly emerging treatment method to deliver a high dose of radiation to the target, utilizing a single dose or a small number of fractions with a high degree of precision within the body' (11). There is no absolute standard for what constitutes a high dose or a small number of fractions, and fractionation schemes can vary according to institutions and physicians. Furthermore, fractionation schemes are partially altered according to medical insurance coverage. In Korea, SBRT has been covered by the National Health Insurance Service when the number of fractions is ≤4 within the body. Therefore, the majority of studies using SBRT to HCC in Korea use three to four fractions (4,12–15). Our current survey revealed that the most common number of fractions was 3, as shown in Fig 2A. On the other hand, the most common number of fractions for the liver lesion according to a survey in the United States was 3 (48%), followed by 5 (38%) (16). The most common number of fractions for primary liver cancer from a survey in Japan was 4, followed by 5 (17). The most common number of fractions for HCC according to Canadian guidelines was 6 (18). Furthermore, compared with conventional radiation therapy, there is variable dose heterogeneity within the PTV in SBRT according to the treatment machine or selected isodose line even though the tumour was prescribed by same radiation dose (19). Eriguchi et al. (20) conducted a prospective multi-institutional study to assess inter-institutional variations in treatment planning for HCC SBRT. Four institutions made a SBRT plan prescribing 40 Gy in five fractions within 95% of the PTV. PTV dose distribution varied among institutions owing to differences in the prescription point; one institution prescribed at the 70% isodose level relative to the global maximum dose, while the other three institutions prescribed at the isocenter. They found that differences in dose distribution between institutions decreased significantly when the dose was prescribed to an isodose line fitted to the PTV surface. The authors suggested detailed dose specifications for multi-institutional study to minimize the variation. Therefore, we need further studies to standardize various fractionation schemes and clarify PTV dose distribution among physicians. A thorough dosimetric analysis of several prospective SBRT studies for HCC (NCT01850368, NCT01850667 and NCT01825824), which currently are conducted by our group, would give some answers.

In the clinical setting, the SBRT dose can be changed on a case-by-case basis. Generally, fixed doses are employed for relatively small tumours (≤3 cm) to administer the necessary minimum dose with sufficient efficacy (the minimum effective dose), and modified doses are employed for relatively larger tumours to deliver the maximum dose if dose constraints to the organ at risk are satisfied (the maximum tolerable dose) (21). In our two clinical scenarios, most physicians decreased total doses, increased the number of fractions or converted into other fractionations such as hypofractionation or conventional fractionation according to the tumour size and baseline CP class. The difference in SBRT doses among physicians can be ascribed to two main reasons. First, we do not yet know the minimum effective dose for HCC SBRT. Kwon et al. (15) reported 3-year LCR of 68% after SBRT with 30–39 Gy/3 fractions. However, Sanuki et al. (22) reported a 3-year LCR of 91% after SBRT with 40 Gy/5 fractions for CP class of A and 35 Gy/5 fractions for CP class of B; there was no significant difference in LCR between dose levels (91% vs. 89%). On the other hand, Bujold et al. (5) showed a significant difference between SBRT doses (24–54 Gy/6 fractions) and 1-year LCR. Jang et al. (23) suggested a dose–response relationship between SBRT dose and LCR: 2-year LCR was 100% for >54 Gy/3 fractions, 78% for 45–54 Gy/3 fractions and 64% for <45 Gy/3 fractions. The minimum effective dose would be between 24 and 60 Gy, but the optimal dose remains unknown. Second, we still do not know the maximum tolerable dose of the liver for HCC SBRT. HCC is a complex neoplasm that grows in a preneoplastic cirrhotic liver, and the CP class, which reflects preexisting liver dysfunction, is considered as a leading cause of death (24). Therefore, we need discrete liver dose constraints for HCC SBRT apart from liver metastases, which have a relatively normal liver function. Although more than half of the physicians selected $V_{15\ \mathrm{Gy}}$ and $V_{17\ \mathrm{Gy}}$ (generally recommended liver dose constraints) in our survey, the remainder had various liver dose constraints; international studies reported the same variability (25). These results suggest that efforts should be made to gather all available data to determine a definite liver dose constraint.

There were some limitations in the current study. First, we obtained the information from the recollections retrieved by the respondents regarding HCC SBRT experiences from the past. Recall bias may have occurred, and, especially, when the respondents started SBRT for HCC may be inaccurate. Second, we used closed-ended questions to get vast and precise information from all respondents because little is unknown about practical patterns for HCC SBRT in Korea before this study. Therefore, the current survey could not focus on definite indication of HCC SBRT. Further surveys composed of open-ended questions by experienced specialist, conferences or well-organized clinical trials should be needed to define the optimal indication of HCC SBRT.

In conclusion, through a national patterns-of-care survey, we discovered a diversity of practical patterns among radiation oncologists in Korea using liver SBRT for HCC patients. Based on the findings of this survey, we need additional prospective studies to standardize the practice and establish Korea-specific practice guidelines for HCC SBRT. Participation in multicentre clinical trials for HCC SBRT would be a great help. A thoroughly described protocol should be prepared to minimize inter-institutional variation.

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Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Conflict of interest statement

None declared.

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