calculated and set around the CTV by 2–5 mm according to the individual measurements for respiratory motion of each institution. Internal margin caused by respiratory motion was reduced by gating, tracking, breath-hold technique, or abdominal compression. Planning target volume (PTV) comprised the CTV, a proper internal margin measured in each patient, and a 5-mm safety margin. The total margin between PTV and GTV was thus 7–15 mm. The irradiated port marginally exceeded PTV by 3–5 mm to secure the surface dose of PTV. Dose calculation was performed using the Clarkson algorithm and heterogeneity correction. A total dose of 45–72.5 Gy (mean, 58.7 Gy) at the isocenter in 3–10 fractions with single doses of 6.25–15 Gy was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Minimum dose in the PTV corresponded to 85–95% of the prescribed dose in most cases. Typical dose/fractionation schedules were 75 Gy in 10 fractions for 42 patients and 48 Gy in 4 fractions for 38 patients. In principal, patients were treated on consecutive days, but some patients were treated every other day. No chemotherapies were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, BED was utilized in a linear-quadratic model (19). Biologically effective dose was here defined as $nd(1 + d/\alpha/\beta)$, with units of Gy, where n is fractionation number, d is daily dose, and α/β is assumed to be 10 for tumors. Biologically effective dose was not corrected with values for tumor doubling time or treatment term. Biologically effective dose was calculated at the isocenter in this study. Median calculated BED was 116 Gy (range, 100–141 Gy).

No restriction was placed on whether the tumor was located peripherally or centrally in the lung, but dose for the spinal cord was limited. Biologically effective dose limitation for spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). Doses for other organs were not restricted.

Evaluation

The objectives of this study were to retrospectively evaluate toxicity, local control rate, and survival rate. Follow-up examinations were performed 4 weeks after treatment first, then patients were seen every 1–3 months. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors by CT (20). Chest CT (slice thickness, 2–5 mm) was usually obtained every 2 to 3 months for the first year and repeated every 4–6 months thereafter. Complete response indicated that the tumor had completely disappeared or was judged to have been replaced by fibrotic tissue. Partial response was defined as a ≥30% reduction in maximum cross-sectional diameter. Distinguishing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered evidence of partial response, so actual complete response rate may have been higher than presented herein. Distinguishing between local recurrence and inflammatory change was also difficult. Here, local recurrence was considered to have occurred only when enlargement of the local tumor continued for >6 months on follow-up CT, obviously positive findings were identified on positron emission tomography, or histologic confirmation was acquired. Findings on CT were interpreted by two radiation oncologists in each case. Absence of local recurrence was defined as locally controlled disease. Lung, esophagus, bone marrow, and skin were evaluated using version 2 of the National Cancer Institute–Common Toxicity Criteria.

Statistical analysis

Cumulative rates of progression-free status at local, regional lymph node, and distant sites and survival were calculated and drawn using Kaplan-Meier algorithms, with day of treatment as the starting point. Subgroups were compared using log–rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using StatView version 5.0 software (SAS Institute, Cary, NC).

RESULTS

All patients completed treatment without obvious complaints. Median durations of observation for all patients and survivors as of final follow-up were 55 and 63 months, respectively.

Local tumor response

Complete response was achieved in 28 patients (32.2%), and partial response was seen in 43 patients (49.4%).

Toxicity

Radiation-induced pulmonary complications of National Cancer Institute–Common Toxicity Criteria (version 2.0) Grade 0, 1, 2, and 3 were noted in 21 (24.1%), 61 (70.1%), 4 (4.6%), and 1 patient (1.1%), respectively. Rib fracture and Grade 3 dermatitis were observed in 4 (4.6%) and 3 patients (3.4%), respectively. All tumors bordered the chest wall. Grade 3 radiation-induced esophagitis was produced in 1 patient, in whom the tumor slightly bordered the esophagus. Maximum esophageal dose in this case was 30 Gy in 5 fractions. No vascular, cardiac, or bone marrow complications had been encountered as of last follow-up. In total, Grade 3 toxicities were identified in 8 patients (9.2%).

No definite second malignancies were found during follow-up, but 1 patient died of acute myelogenous leukemia 3.7 years after completing SBRT.

Recurrence

Local recurrence, lymph node metastases, and distant metastases occurred in 8 (9.2%), 13 (14.9%), and 19 cases (21.8%), respectively.

Cumulative local progression–free rate curves according to stage are shown in Fig. 1. Cumulative local progression–free rate after 5 years was 86.7% (95% confidence interval [CI], 78.3–94.9%) for total cases. Cumulative local progression–free rate at 5 years was 92.0% (95% CI, 83.8–99.6%)

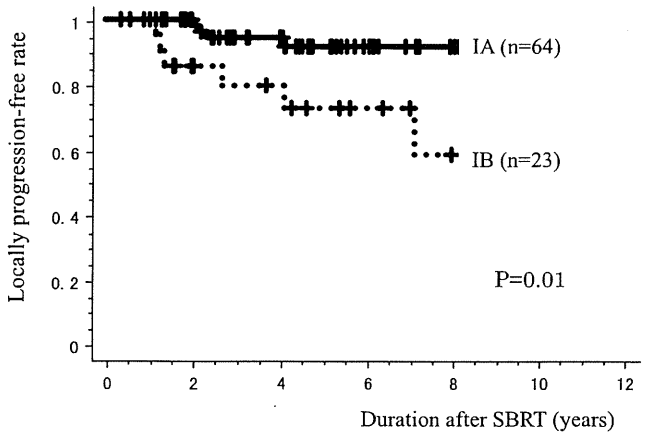

Fig. 1. Cumulative local progression–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

for the Stage IA subgroup, significantly superior ($p = 0.01$) to that for the Stage IB subgroup (73.0%; 95% CI, 52.2–93.7%). Five-year local progression–free rates were not significantly different between adenocarcinoma (80.9%; 95% CI, 68.7–93.1%) and squamous cell carcinoma (95.5%; 95% CI, 86.7–100.0%). One patient who developed local recurrence underwent surgery and has remained healthy for more than 3 years after operatively. The operation method was upper lobectomy and mediastinal lymphadenectomy, and they were performed safely without any trouble.

Cumulative curves of regional lymph node and distant metastases–free rates according to stage are shown in Figs. 2 and 3, respectively. The 5-year lymph node metastasis–free rate and distant metastasis–free rate for total cases was 85.3% (95% CI, 77.6–93.0%) and 75.1% (95% CI, 64.8–85.4%], respectively. No significant difference was identified between Stage IA and IB subgroups.

In patterns of regional nodal recurrence, 8 patients (61.5%) showed nodal failure alone, 2 patients (15.4%) had nodal failure combined with local failure, and 3 patients (23.1%) showed nodal failure combined with distant metastases.

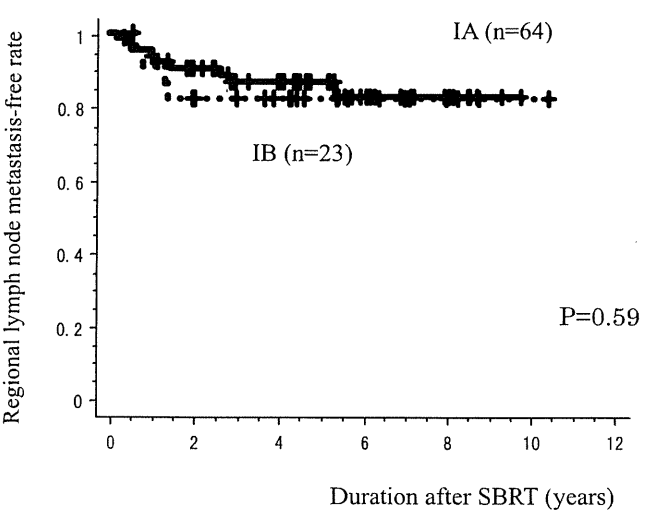

Fig. 2. Cumulative regional lymph node metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

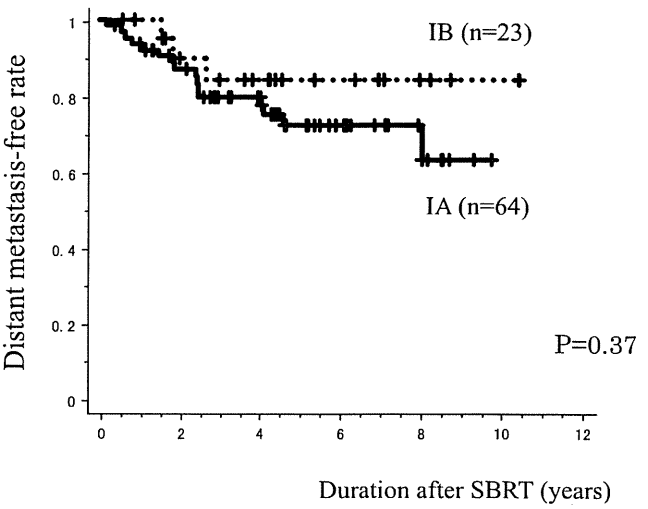

Fig. 3. Cumulative distant metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

Survival

Overall and cause-specific 5-year survival rates for total cases were 69.5% (95% CI, 58.8–80.1%) and 76.1% (95% CI, 65.9–86.3%), respectively. Overall and cause-specific survival curves according to stage are shown in Figs. 4 and 5, respectively. Five-year overall survival rate was 72.0% (95% CI, 59.6–84.4%) in Stage IA patients and 63.2% (95% CI, 42.7–83.6%) in Stage IB patients. A marginal but nonsignificant ($p = 0.14$) difference was found between overall survival rates of Stage IA and IB groups. In terms of histology, overall 5-year survival rate was 72.2% (95% CI, 59.2–85.2%) in the adenocarcinoma subgroup and 60.8% (95% CI, 38.4–83.2%) in the squamous cell carcinoma subgroup.

DISCUSSION

Exposing a tumor to a higher dose of radiation without increasing adverse effects can be achieved using stereotactic techniques. Stereotactic irradiation is an approach using

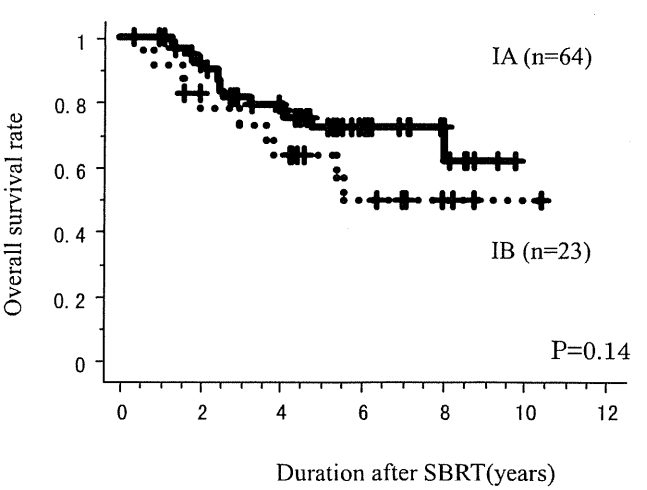

Fig. 4. Cumulative overall survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

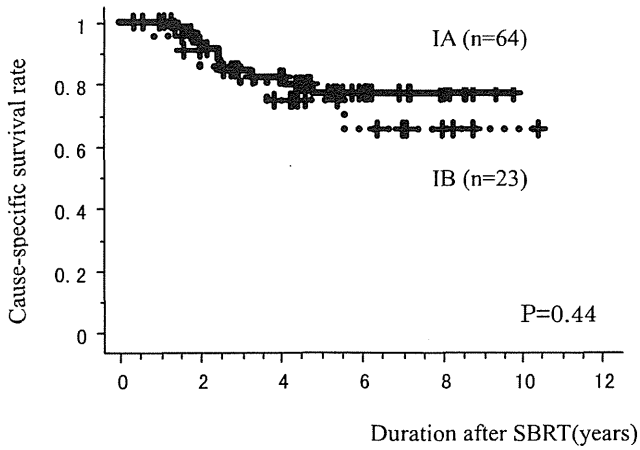

Fig. 5. Cumulative cause-specific survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

multiple noncoplanar convergent beams, precise localization with a stereotactic coordinate system, rigid immobilization, and single high-dose treatment, maximizing delivery to the tumor and minimizing the exposure of normal tissue. This approach can also substantially reduce overall treatment time from several weeks of conventional radiotherapy schedule to a few days, offering an important advantage to the patient. Stereotactic irradiation techniques are well established for the treatment of intracranial malignancies, but use in extracranial malignancies has been considered problematic because of the issues of fixation and internal motion. In 1994, Blomgren *et al.* (21) described a technique of SBRT using a custom-made body cast and stereotactic coordinates. In 1996, Uematsu *et al.* (22) reported a CT–linear accelerator unit sharing a common couch, enabling image-guided fractionated SBRT without rigid immobilization. Since verification of the effects and safety of SBRT for lung cancer (12), this treatment method has rapidly been adopted in many institutions (Table 2) (12–17, 23, 24). Although various fractionation schedules are undergoing evaluation around the world, a frequently used BED prescribed for tumors with SBRT for Stage I NSCLC in Japan has been set at a little over 100 Gy, as recommended in our previous study (18). However, concerning determination of the truly optimal dose of SBRT for Stage I NSCLC, many problems and controversies remain, such as dose-calculation algorithms (16), inhomogeneity corrections, essential dose for tumor control (24), and dose constraints for organs at risk (25, 26).

Although a number of articles on SBRT for Stage I NSCLC have been published, duration of follow-up in most cases has not been sufficiently long, and almost all treated patients were medically inoperable. The present study thus provides data on two important areas.

One was cumulative local recurrence and metastatic rates with a long duration of follow-up after SBRT. Rates of local control and metastases depend largely on the duration of follow-up and generally deteriorate as the duration of follow-up increases. Furthermore, recurrence rates have been reported in numerous articles, but most of them were crudely calculated rate. We have presented 5-year cumulative local control, regional lymph node recurrence–free and distant metastasis–free rates, calculated using Kaplan-Meier methods. The local progression–free rate in our results was unsatisfactory, particularly for the T2 tumor subgroup. The Japanese Clinical Oncology Group (JCOG) has thus started a multi-institutional dose-escalation study for Stage IB NSCLC patients (JCOG 0702).

Another meaningful result was the overall survival rate with a longer follow-up duration, allowing comparison between SBRT and surgery. Although the survival rate in this study was less than in our previous reports, we consider this information worth reporting, because median duration of follow-up was almost 5 years. Uematsu *et al.* (12) reported a 3-year overall survival rate of 86% in 29 medically operable patients with Stage I NSCLC, but the number of patients was small, and follow-up duration was relatively short. Because the number of medically operable patients treated with SBRT was very small in individual institutions, the present study collated the data of operable patients from multiple institutions. Whether the survival rate of SBRT was lower than that of surgery could not be clarified from our results. Representative 5-year overall survival rates of surgery for clinical

Table 2. Reports of SBRT for Stage I NSCLC

First author (reference)	*N*	Total dose (Gy)	Single dose (Gy)	BED (Gy)	Median follow-up (mo)	Local recurrence (%)	3-y overall survival (%)
Uematsu (12)	50	72	7.2	124	60	6*	6
Nagata (13)	42	48	12	106	52	3*	82
Onimaru (14)	28	48	12	106	27	36†	82 (Stage IA) 32 (Stage IB)
Onishi (15)	26	72	7.2	124	24	8*	75
Takeda (16)	63	50	10	100	31	5†	90 (Stage IA) 63 (Stage IB)
Koto (17)	31	45–60	7.5–15	105–113	32	29*	72
Hof (23)	10	19–26	19–26	55–94	15	40*	37
Fakiris (24)	47	60–66	20–22	180–211	50	12†	43

Abbreviations: SBRT = stereotactic body radiotherapy; NSCLC = non–small-cell lung cancer; BED = biologically effective dose ($\alpha/\beta = 10$).
* Crude data.
† Cumulative data calculated with Kaplan-Meier method.

Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy.
Values are percentages.

Stage IA and IB NSCLC are listed in Table 3 (1–3), ranging approximately 60–75% for Stage IA and 40–60% for Stage IB. We cannot conclude that the survival rate for SBRT is equivalent to that for surgery, because the present data for SBRT are based on a retrospective study and small sample size. However, the background of patients treated by SBRT in this study seems likely to have included worse prognostic factors than those in patients treated surgically. Concerning the size and characteristics of tumors, good prognostic factors such as smaller tumor size (27) or lower-density mass (so-called ground-glass opacities) (28) might be more frequently included in patients treated with surgery, because the determination of histological malignancy before SBRT was difficult for such tumors. In addition, median age of patients treated by surgery was approximately 10 years younger in the surgical series (median, 60–65 years) than in the SBRT series (median, 75 years). We therefore believe that survival rates for SBRT in medically operable patients are potentially comparable to those for surgery.

Regarding treatment-related toxicity, the rate of severe (Grade ≥3) acute and short-term chronic complications after SBRT was very low and acceptable, despite the high age of those patients (median, 74 years) in our experience. In results for pulmonary lobectomy, Deslauriers *et al.* (29) reported much higher mortality and morbidity rates that increased with aging. In other reports, mortality rates for patients aged >70 years old after pulmonary lobectomy were 7.6% (30). Even though improvements of mortality and morbidity of surgery may have recently been achieved (31), in particular under a technique of video-assisted thoracoscopic lobectomy (32), we consider SBRT as a safer and less invasive treatment modality than surgery, at least for peripherally located lung tumor up to 5 years after treatment. However, reports of SBRT for centrally located lung tumor have shown a comparably high risk (25, 26), and long-term chronic toxicity remains unclear. A longer and larger follow-up of SBRT is needed.

We thus consider that SBRT may offer a useful option for initial radical treatment of at least peripheral Stage IA NSCLC, not only for medically inoperable patients but also for operable patients. However, regarding centrally located or large T2 tumors, surgery must still be recommended as the first choice of treatment until further data can be accumulated. Although we encountered only 1 case in the present study, pulmonary lobectomy and mediastinal lymph node resection were performed without difficulty for a locally recurring tumor after SBRT. Surgery might be an option as salvage therapy for locally recurrent cases after radical SBRT for Stage I NSCLC.

In Japan, the number of patients treated with SBRT has exploded, especially since SBRT for lung cancer has been covered by the national health insurance since 2004. A Phase II multi-institutional study of JCOG researching the efficacy and toxicity of SBRT for both medically operable and inoperable Stage IA NSCLC patients (JCOG 0403) started in 2004, and patient entry was completed in October 2008. A total of 90 medically inoperable and 65 operable patients have been enrolled. In the United States, a Phase II multi-institutional study of SBRT for only medically inoperable Stage I NSCLC patients (Radiation Therapy Oncology Group 0236) has been ongoing.

Even multi-institutional Phase II studies of SBRT for Stage I NSCLC may have inevitable selection bias compared with surgical series. A prospective randomized trial is essential to conclude whether outcomes of SBRT for medically operable patients are truly comparable to those of surgery. A protocol for randomized studies comparing SBRT with surgery for Stage I NSCLC has been initiated (33) but has not progressed. Such a randomized study is likely to prove very difficult to perform, because most patients may hope for more minimally invasive therapy, such as SBRT. Many more experiences for more patients with a longer follow-up duration are thus needed to confirm the safety and effects of SBRT as a radical treatment for operable Stage I NSCLC. If the experience of SBRT for medically operable Stage I NSCLC matures and produces no poor results in future, SBRT will have a marked impact on standard treatment procedures for lung cancer and provide good news for Stage I lung cancer patients, the prevalence of whom is likely to increase.

In conclusion, treatment results of SBRT reviewed from a Japanese multi-institutional database showed that SBRT is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate of SBRT is potentially comparable to that of surgery.

REFERENCES

1. Mountain CF. The international system for staging lung cancer. *Semin Surg Oncol* 2000;18:106–115.
2. Naruke T, Tsuchiua R, Kondo H, *et al.* Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: The Japanese experience. *Ann Thorac Surg* 2001;71:1759–1764.
3. Asamura H, Goya T, Koshiishi Y, *et al.* A Japanese Lung Cancer Registry study: Prognosis of 13,010 resected lung cancers. *J Thorac Oncol* 2007;3:46–52.
4. Sibley GS, Jamieson TA, Marks LB, *et al.* Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: The Duke experience. *Int J Radiat Oncol Biol Phys* 1998;40:149–154.

5. Krol AD, Aussems P, Noordijk EM, *et al.* Local irradiation alone for peripheral stage I lung cancer: Could we omit the elective regional nodal irradiation? *Int J Radiat Oncol Biol Phys* 1996;34:297–302.
6. Hayakawa K, Mitsuhashi N, Saito Y, *et al.* Limited field irradiation for medically inoperable patients with peripheral stage I non-small cell lung cancer. *Lung Cancer* 1999;26:137–142.
7. Jeremic B, Shibamoto Y, Acimovic L, *et al.* Hyperfractionated radiotherapy alone for clinical stage I nonsmall cell lung cancer. *Int J Radiat Oncol Biol Phys* 1998;38:521–525.
8. Mehta M, Scringer R, Mackie R, *et al.* A new approach to dose escalation in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001;49:23–33.
9. Kong FM, Haken RK, Schipper MJ, *et al.* High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small cell lung cancer: Long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324–333.
10. Narayan S, Henning GT, Haken RK, *et al.* Results following treatment to dose of 92.4 or 102.9 Gy on a phase I dose escalation study for non-small cell lung cancer. *Lung Cancer* 2004;44: 79–88.
11. Fang LC, Komaki R, Allen P. Comparison of outcomes for patients with medically inoperable Stage I non-small-cell lung cancer treated with two-dimensional vs. three-dimensional radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;66:108–116.
12. Uematsu M, Shioda A, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiography for stage I non-small-cell lung cancer: 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
13. Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II study of 48Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–1431.
14. Onimaru R, Fujino M, Yamazaki K, *et al.* Steep dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;70:374–381.
15. Onishi H, Kuriyama K, Komiyama T, *et al.* Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: Patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner. *Lung Cancer* 2004;45:45–55.
16. Takeda A, Sanuki N, Kunieda E, *et al.* Stereotactic body radiotherapy for primary lung cancer at a dose of 50Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. *Int J Radiat Oncol Biol Phys* 2009;73:442–448.
17. Koto M, Takai Y, Ogawa Y, *et al.* A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol* 2007;85:429–434.
18. Onishi H, Shirato H, Nagata Y, *et al.* Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2(7 Suppl. 3): S94–S100.
19. Yaes RJ, Patel P, Maruyama Y. On using the linear-quadratic model in daily clinical practice. *Int J Radiat Oncol Biol Phys* 1991;20:1353–1362.
20. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
21. Blomgren H, Lax I, Naslund I, Svanstrom R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 1995;34:861–870.
22. Uematsu M, Fukui T, Shioda A, *et al.* A dual computed tomography and linear accelerator unit for stereotactic radiation therapy: A new approach without cranially fixated stereotactic frame. *Int J Radiat Oncol Biol Phys* 1996;35:587–592.
23. Hof H, Herfarth KK, Munter M, *et al.* Stereotactic single-dose radiotherapy of stage I non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2003;56:335–341.
24. Fakiris AJ, McGarry RC, Yiannoutsos CT, *et al.* Stereotactic body radiation therapy forearly-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677–682.
25. Timmerman R, McGarry R, Yiannoutsos C, *et al.* Excessive toxicity when treating central tumors in phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833–4849.
26. Song SY, Choi W, Shin SS, *et al.* Fractionated stereotactic body radiation therapy for medically inoperable stage I lung cancer adjacent to central large bronchus. *Lung Cancer* 2009;66:89–93.
27. Akakura N, Mori S, Okuda K, *et al.* Subcategorization of lung cancer based on tumor size and degree of visceral pleural invasion. *Ann Thorac Surg* 2008;86:1084–1091.
28. Asamura H, Suzuki K, Watanabe S, *et al.* A clinicopathological study of resected subcentimeter lung cancers: A favorable prognosis for ground glass opacity lesions. *Ann Thorac Surg* 2003; 76:1016–1022.
29. Deslauriers J, Ginsberg RJ, Dubois P, *et al.* Current operative morbidity associated with elective surgical resection for lung cancer. *Can J Surg* 1989;32:335–339.
30. Thomas P, Piraux M, Jacques LF, *et al.* Clinical patterns and trends of outcome of elderly patients with bronchogenic carcinoma. *Eur J Cardiothorac Surg* 1998;13:266–274.
31. Nagai K, Yoshida J, Nishimura M. Postoperative mortality in lung cancer patients. *Ann Thorac Cardiovasc Surg* 2007;13: 373–377.
32. Whitson BA, Groth SS, Duval SJ, *et al.* Surgery for early stage non-small cell lung cancer: A systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg* 2008;86:2008–2016.
33. Hurkmans CW, Cuijpers JP, Largerwaard FJ, *et al.* Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: Report from the Quality Assurance Working Party of the randomized phase III ROSEL study. *Radiat Oncol* 2009;4:1.

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 660–669, 2011
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0360-3016/$ - see front matter

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doi:10.1016/j.ijrobp.2010.10.004

CRITICAL REVIEW

STEREOTACTIC RADIOTHERAPY OF PRIMARY LUNG CANCER AND OTHER TARGETS: RESULTS OF CONSULTANT MEETING OF THE INTERNATIONAL ATOMIC ENERGY AGENCY

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To evaluate the current status of stereotactic body radiotherapy (SBRT) and identify both advantages and disadvantages of its use in developing countries, a meeting composed of consultants of the International Atomic Energy Agency was held in Vienna in November 2006. Owing to continuous developments in the field, the meeting was extended by subsequent discussions and correspondence (2007–2010), which led to the summary presented here. The advantages and disadvantages of SBRT expected to be encountered in developing countries were identified. The definitions, typical treatment courses, and clinical results were presented. Thereafter, minimal methodology/technology requirements for SBRT were evaluated. Finally, characteristics of SBRT for developing countries were recommended. Patients for SBRT should be carefully selected, because single high-dose radiotherapy may cause serious complications in some serial organs at risk. Clinical experiences have been reported in some populations of lung cancer, lung oligometastases, liver cancer, pancreas cancer, and kidney cancer. Despite the disadvantages expected to be experienced in developing countries, SBRT using fewer fractions may be useful in selected patients with various extracranial cancers with favorable outcome and low toxicity. © **2011 Elsevier Inc.**

Stereotactic body radiation therapy, Non–small-cell lung cancer, Lung metastases, Liver cancer, Pancreatic cancer, Kidney cancer.

INTRODUCTION

Cancer is one of the major health concerns worldwide. The burden of cancer is increasing globally, with 20 million new cases expected per year in 2020, half of which will be in developing countries (1). The inability to cope with the growing economic and societal burden of cancer is emblematic of the tremendous health disparities reflected in developing countries, which have only 5% of the global resources spent on cancer (2–3).

The proportion of cancer patients in developing countries requesting radiotherapy (RT) is likely higher than in regions of high income because of the types of cancers and the stages at which these tumors are diagnosed (4). Moreover, patients in developing countries are dealing with some issues that are not common in the developed world. They include patient transportation to the facility (5), social support, accessible local housing, and noncompliance with treatment. It was shown (6) that the use of short courses in selected patients could be cost effective and convenient, especially for patients coming from remote areas.

Although many countries have not yet established RT service, others have aging RT services, which are usually restricted to a few centers, mainly concentrated in large urban areas. RT is affordable for developing countries with large populations, but some regions with small populations have not invested in RT (7–10). Emerging new technologies for cancer treatment, however, are spreading widely, in both developed and developing countries. One of these, stereotactic body radiotherapy (SBRT), has been increasingly used in recent decades.

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Conflict of interest: none.

Received April 30, 2010, and in revised form Sept 30, 2010. Accepted for publication Oct 2, 2010.

The International Atomic Energy Agency (IAEA) has a crucial role in both developing new RT facilities and upgrading existing facilities, including equipment and human resources in developing countries. By organizing meetings of experts, the IAEA gathers advice in RT to establish RT facilities in member states. With such an aim, a meeting of consultants was held in Vienna in November 2006 to advise the IAEA on the state of the art of the use of SBRT in primary lung tumors and other body tumors. This article represents a summary of that meeting and subsequent (2007–2010) communication between experts on the recent developments in SBRT deemed necessary because of the fast developments in the field.

Stereotactic radiation characteristics

Characteristics attractive to developing nations. Several characteristics would make SBRT attractive to developing nations. Shortened treatment time with fewer fractions than usually used in developing countries would be a major consideration. This in turn would generally enable improved access to RT treatments in departments worldwide. In addition, shorter treatment (outpatient or inpatient) would also be more cost effective for both patients and hospitals. This would be realized by lessening travel from prolonged distances to and from hospitals, and secondly for hospitals having limited inpatient capabilities. Other attractive characteristics would include improved overall results such as local control, overall survival, and disease-specific survival. Lower toxicity, in addition, would also be an important issue from the standpoint of both better quality of life and less costly symptomatic care (including frequent hospitalization in a patient population having a notorious record of having excessive comorbidities) needed in such cases.

Obvious barriers to implementation in developing nations. There may be several barriers for successful implementation of SBRT of lung cancer in developing countries. They can be broadly separated into pretreatment and treatment issues, including low incidence in certain regions such as sub-Saharan Africa. The lack of modern and comprehensive diagnostic tools, such as computed tomography (CT) and positron emission tomography, would largely jeopardize appropriate diagnosis and staging of potential candidates. In addition, the vast majority of patients would fall into a locally advanced or metastatic category because of a lack of screening and early detection programs that may result in identification of suitable cases, *i.e.,* those having Stage I non–small-cell lung cancer. Of treatment-dependent obstacles, capital costs for obtaining an immobilization system would be the major issue, assuming that existing external-beam RT machines (primarily linear accelerators) have been properly maintained. Lack of previous exposure and experience with three-dimensional RT, seen as the logical parent of SBRT, may be an important obstacle. Barriers to successful implementation of SBRT also include insufficient staffing, inadequate training of personnel, and lack of a dedicated team for introducing and implementing this technique.

CURRENT STATUS OF SBRT DELIVERY IN THE DEVELOPED WORLD

Historical aspects and early experience

Intracranial stereotactic radiosurgery (SRS) was a novel treatment method when introduced in the middle of the 20th century, with conceptual parallels to brachytherapy in regard to the tight spatiotemporal distribution in dose delivery. The clinical experience with intracranial SRS, together with the technical developments in conventional RT, initiated the development of SBRT characterized by a very high dose per fraction, delivered in a short time. This was started at the Swedish Karolinska University hospital in 1991 with tumors in the liver and lungs (11, 12). In parallel the method was developed in Japan and clinically introduced in 1994 for lung tumors. During the last 5 years of the 1990s, SBRT was introduced in several centers in Europe, Japan, and the United States (13–19). The early reports had already shown very promising results with regard to local control and toxicity for the hypofractionation schedules that were adopted, with 10 to 15 Gy per fraction given in a few fractions during a short time (15, 20). However, owing to the new aspects introduced in SBRT, clinical experience was initially gathered at a very slow rate, and it was only during the past decade that outcome data from several centers were available to confirm the initial promising results.

Experience in primary lung tumors

Many studies with SBRT were conducted around the world in treating both primary and metastatic cancers within the lungs because of their high prevalence, the high rates of cancer-associated deaths, and the desire for more effective treatments. The experience in treating primary lung cancer using SBRT has been obtained mainly in patients unfit for surgical resection (*i.e.,* medically inoperable patients). Furthermore, nearly all reports described outcomes in patients with Stage I disease, particularly for peripheral tumor locations. Inasmuch as medically inoperable lung cancer patients are at risk for death of other causes, survival in these patients is ultimately compromised. Still, the benefits of SBRT were demonstrated by dramatically improved rates of local control.

Local tumor response. The local control rates of primary lung cancer with SBRT have been previously reported by several authors (Table 1): 94 % (47/50) for 50 to 60 Gy in five fractions with a median follow-up time of 36 months (21, 23); 92 % (22/24) for 60 Gy in eight fractions with a median follow-up time of 24 months (22, 24) 87 % (30/37) for 60 Gy in three fractions with a median follow-up time of 15 months (19); 85% for 48 to 60 Gy in eight fractions with a median follow-up time of 17 months (25); 95% for 45 to 56.2 Gy in three fractions with a median follow-up time of 10 months (26); 90% for 30 to 40 Gy in

Table 1. Local control rates of stereotactic radiotherapy for primary lung cancer

Study	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up time
Uematsu *et al.*, 2001 (21, 23)	50–60	10	80% margin	94%(47/50)	36 months
Arimoto *et al.*, 1998 (24)	60	7.5	Isocenter	92%(22/24)	24 months
Timmerman *et al.*, 2003 (19)	60	20	80% margin	87%(30/37)	15 months
Onimaru *et al.*, 2003 (25)	48–60	6–7.5	Isocenter	80%(20/25)	17 months
Wulf *et al.*, 2004 (26)	45–56.2	15–15.4	80% margin	95%(19/20)	10 months
Nagata *et al.*, 2005 (28)	48	12	Isocenter	97%(44/45)	30 months
Lee *et al.*, 2003 (27)	30–40	10	90% margin	90%(8/9)	21 months
Fakiris *et al.*, 2009 (29)	60–66	20–23	80% margin	88%(70)	50 months
Baumann *et al.*, 2009 (30)	45	15	67% margin	92%(57)	35 months
Timmerman *et al.*, 2010 (31)	60	20	80% margin	98%(54/55)	36 months

four fractions with a median follow-up time of 21 months (27); 97% (44/45) for 48 Gy in four fractions with a median follow-up time of 22-30 months (28); 88% for 60 to 66 Gy in three fractions with a median follow-up time of 50 months (29); and 92% for 45 Gy in three fractions with a median follow-up time of 35 months (30). The Radiation Therapy Oncology Group (RTOG) 0236 demonstrated a very good 3-year local control rate that was as high as 98% (31). Even though the definition of local control is different between each trial, a biologic effective dose (BED) larger than 100 Gy may be effective for SBRT of solitary lung cancers with a local control rate above 85%.

Survival. In a series of Stage IA disease (T1N0M0), the 1-year and 5-year local relapse-free survival rates were 100% and 95%. The disease-free survival rates after 1, 3, and 5 years were 80%, 72%, and 72%, respectively, and the overall survival rates were 93%, 83%, and 83%, respectively. In the Stage IB (T2N0M0) series of Nagata *et al.* (28), local relapse-free survival rates were 100%. The disease-free survival after 1, 3, and 5 years were 92%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72$, and 72%, respectively. Onishi *et al.* (32) reported the results for 13 institutions in Japan, which summarized 245 patients: 155 with Stage IA lung cancer and 90 with Stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED = 100 Gy were 90% for Stage IA and 84% for Stage IB disease, and their clinical results were as good as those obtained by surgery.

Toxicities. The great concern of pulmonary toxicity with SBRT treatment was moderated by the very low rates of complications in early studies. Most pulmonary complications are less than Grade 2 according to the National Cancer Institute Common Terminology Criteria version 2.0. It is not uncommon for patients to experience rib fracture or chest wall pain months after SBRT, especially if tumors adjacent to the chest wall have been treated. Some of these patients, but not all, will have pleural effusions associated with the chest wall pain. The problem seems mostly to be self limited, and conservative management with over-the-counter analgesics or anti-inflammatory medicines is typically effective.

However, a few serious complications have recently been reported by several institutions in Japan (33). These include Grade 5 pulmonary complications, radiation pneumonitis, hemoptysis, and radiation esophagitis. Most cases of Grade 5 radiation pneumonitis were accompanied with interstitial pneumonitis.

Another concern of toxicity was the effects on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord, for which a hypofractionated dose had not been followed up for a sufficiently long time. Lethal pulmonary bleeding and esophageal ulcer have been previously reported (33). Timmerman *et al.* also reported a series of complications with SBRT (34). Chang *et al.* reported on safely treating central tumors considering dose constraints with the SBRT technique (35). Nonetheless, central tumors adjacent to mediastinal organs should be carefully considered (36). Toxicities as reported in several articles are shown in Table 2.

The most important issue is to maintain the dose constraints of organs at risk (OAR) to avoid serious complications. The dose constraints of the OAR, including the spinal cord, pulmonary artery, bronchus, and heart under the Japan Clinical Oncology Group (JCOG) 0403 protocol, are shown in Table 3. The RTOG has enacted normal tissue

Table 2. Clinical toxicities after stereotactic radiotherapy for primary lung cancer

Study	Number of cases	Lung ≥Grade 3	Lung Grade 5	Other Grade 5
Uematsu *et al.*, 2001 (23)	50	0%	0%	
Arimoto *et al.*, 1998 (24)	24	NA	0%	
Lee *et al.*, 2003 (27)	28	0	0%	
Onimaru *et al.*, 2003 (25)	45	2%	0%	Esophagus
Wulf *et al.*, 2004 (26)	61	0	0%	
Nagata *et al.*, 2005 (28)	45	0	0	
Timmerman *et al.*, 2006 (34)	70	20%	9%	Hemoptysis, pericarditis
J-CERG, 2009 (33)	2,106	NA	0.6%	Esophagus, hemoptysis

Table 3. Dose and volume constraints for organs at risk in stereotactic body radiotherapy of lung tumors according to Japan Clinical Oncology Group 0403

Organ	Dose	Volume	Dose	Volume
Lung	40 Gy	≤100 cc	MLD	≤18 cc
	V_{15}	≤25%	V_{20}	≤20%
Spinal cord	25 Gy	Maximum		
Esophagus	40 Gy	≤1 cc	35 Gy	≤10 cc
Pulmonary artery	40 Gy	≤1 cc	35 Gy	≤10 cc
Stomach	36 Gy	≤10 cc	30 Gy	≤100 cc
Intestine	36 Gy	≤10 cc	30 Gy	≤100 cc
Trachea, main bronchus	40 Gy	≤10 cc		
Other organs	48 Gy	≤1 cc	40 Gy	≤10 cc

Abbreviation: MLD = Mean Lung Dose, Other organs do not include chest wall & liver.

constraints for RTOG 0618 treating operable patients with early-stage primary lung cancer (Table 4).

Clinical trials. Prospective Phase II testing of SBRT in operable patients is currently ongoing in Japan (JCOG 0403) and the United States (RTOG protocol 0618). In medically inoperable patient groups, a Nordic multi-institutional consortium is comparing three-fraction SBRT to conventional RT in an ongoing randomized Phase II study. The RTOG has finished a Phase II study of three-fraction SBRT for peripheral tumors and is planning a Phase I study with five fractions in patients with central tumors. Finally, the JCOG is finishing a Phase II study using a four-fraction treatment for peripheral tumors and is starting a Phase II study using a higher dose specifically for T2 tumors as JCOG 0701.

Experience in metastatic lung tumors

The experience in treating lung metastasis has been mostly with oligometastases. In contrast to patients with primary lung cancer, patients with metastases do not inherently have poor pulmonary function secondary to tobacco abuse. As such, the toxic effects of treatment would not be expected to be identical between these differing populations. In addition, there is increasing evidence that it may be more difficult to attain local control in metastatic tumors than in primary lung cancer. This would argue for a higher treatment dose (controlled for tumor volume) for metastatic tumors than for primary presentations. Unfortunately, the results of treating lung metastases were frequently included in the reports of patients treated with primary lung cancers, making interpretations of the results more difficult (20, 37–39). Recently a few articles were published that focused on lung metastases (40, 41). Still, SBRT has a relatively high rate of local control per lesion, making it an effective treatment for selected patients with oligometastases.

Table 4. Dose constraints for normal tissue related to steepness of dose gradients from target according to Radiation Therapy Oncology Group 0618 for stereotactic body radiotherapy in operable patients with lung cancer

Organ	Volume	Dose (cGy)
Spinal cord	Any point	18 Gy (6 Gy/fraction)
Esophagus	Any point	27 Gy (9 Gy/fraction)
Ipsilateral brachial plexus	Any point	24 Gy (8 Gy/fraction)
Heart/pericardium	Any point	30 Gy (10 Gy/fraction)
Trachea and ipsilateral bronchus	Any point	30 Gy (10 Gy/fraction)
Whole lung (right & left)	V_{20}	Less than 5–10% of total lung volume
Skin	Any point	24 Gy (8 Gy per fraction)

Experience in liver tumors

Treatment of liver tumors is the second highest indicator for SBRT. Surgical data have shown that local treatment of liver tumors—mostly hepatocellular carcinoma and metastases—can be curative in up to 25–30% of patients if patient selection is appropriate (42). Nevertheless a significant proportion of patients will not be suitable for surgery because of age, medical comorbidity, or intrahepatic localization of the tumor (bilobar, adjacent to large vessels/portal structures). For these cases, SBRT is completely noninvasive and compares favorably with actuarial local control rates of at least 80% after 2 years (16, 20, 43, 44). Acute toxicity is mild. Clinically relevant subacute or late toxicities are not reported, if OAR have been kept out of the high dose area. Nevertheless, local control is dependent on dose, with recurrences occurring even after years, (*e.g.,* with single doses below 26 Gy/isocenter or 3 × 10 Gy/planning target volume [PTV] enclosing 65% isodose) (45, 46). By contrast, some authors have shown that significantly higher doses can be applied safely, such as single doses above 30 Gy/isocenter or 3 × 20 Gy/PTV enclosing 80% isodose, if the normal tissue dose constraints are respected (46–49).

Experience in retroperitoneal (pancreas and kidney) tumors

Abdominal retroperitoneal tumors pose a difficult challenge in view of their proximity to the poorly tolerant bowel. In the case of pancreas tumors, trials have shown conflicting results about the benefit of therapy. Although Hoyer *et al.* indicated little benefit and increased toxicity in patients treated with 45 Gy in three fractions (50), Koong *et al.* used a single dose ranging from 15 to 25 Gy and were able to control tumors in most patients with acceptable toxicity (51, 52).

Although renal cancers are thought to be radioresistant when treated with conventional fractionation schedules, Wersaell *et al.* found extremely high rates of local control with a three- to four-fraction SBRT regimen (53). These results concurred with the high local control rates observed when SRS with a large dose per fraction was used to treat brain metastases of the same histology.

Biology of dose delivery to tumor and normal tissues

Unlike normofractionated RT, the biologic purpose of SRT is for lethal rather than sublethal cell damage in the

high-dose area without repair. Additionally, because of the short overall treatment time (single dose, hypofractionation within 1 to 3 weeks), avoiding the repopulation of tumor cells is another advantage. On the other hand, the presumption is that reoxygenation and redistribution of cells in the cell cycle will not occur with the prescribed dose. The OAR are prevented from serious damage by sparing these tissues from the high-dose area.

Besides dose escalation trials for lung and liver tumors (47, 49), prospective institutional-based reports on the clinical results of SBRT have been published. Unfortunately, comparison of these results is difficult because different dose fractionation schedules have been used, and there is lack of uniformity in normalization and prescribed doses. To overcome this problem, some authors used the BED based on the formula BED (Gy) = dose/fraction × fraction number (1 + fraction dose / α/β using an α/β of 10 Gy for tumor tissue (54, 55). They found a BED of about 100 Gy to be appropriate to achieve a tumor control probability of about 90% for lung tumors. Because it has not been proved that the LQ (linear quadratic) model will be reliable at such high fraction doses, other radiobiologic models might be better suited to predict the effect of SBRT, including modifications of the multitarget model (56).

MINIMUM METHODOLOGY/TECHNOLOGY REQUIREMENTS

Imaging for planning

Imaging for treatment planning is usually based on CT data, whereas magnetic resonance imaging or positron emission tomography can assist this purpose. Before definite scanning, potential breathing mobility has to be evaluated. Depending on the method used to decrease breathing mobility, the amount of motion should be analyzed (it has to be performed to determine the appropriate margins for PTV definition). This can be done by either four-dimensional CT, multislice CT, dynamic scans (repeated scans at the same couch position), or evaluation of the target position during maximum inspiration and expiration. Although this approach is based on slices, which show the scanned tumor position in a very short (<1 second) time, resulting in a sharp image, the target can also be scanned by slow CT. With this technique the tumor is scanned very slowly (*e.g.*, scan time for a slice of 3 seconds). The image shows a blurred shape of the target, including and depending on internal motion (57), which represents the orbit of the moving target. This technique might have advantages, especially when cone-beam CT is used for target verification before irradiation, because the slow scan time (about 1 minute) will cause the shape of the target to also seem blurred (58).

Planning processes

Clinical experience from SBRT has indicated that geometric errors (of a magnitude that is not too uncommon in RT) may lead to more severe consequences than errors in dose delivery. Thus, if priorities need to be determined, geometric aspects should be emphasized more than dose aspects in the planning and delivery processes of SBRT.

Treatment planning in SBRT is done on commercial treatment planning systems, which are also used for RT planning in general. The CT data must account for the different densities in the body for the dose calculation. For dose calculation of tumors in the lungs, pencil beam algorithms have a limited accuracy but are acceptable for use (59). Point kernel–based superposition/convolution algorithms give a more accurate estimate of the dose to the tumor and surrounding lung tissue (60). The error in the dose calculation for tumors in the lungs is reduced if the photon energy is restricted a maximum of 6 MV. Small field sizes are often used in SBRT because of the small size of the PTV. Thus, accurate beam modeling is important (both profiles and depth doses) for field sizes down to 3 cm × 3 cm, preferably down to 2 cm × 2 cm. Image registration tools for the geometric verification process, dose–volume histogram calculation tools, and tools (for example rulers) to calculate the position of the isocenter in the reference system defined by the fiducials must be included.

Radiation beam delivery equipment

Clinical experience with SBRT stems primarily from the use of conventional linear accelerators, and to a lesser extent from more specialized accelerators, but not from the use of conventional cobalt units. The latter is not recommended for SBRT because of the lack of clinical experience and the inferior physical characteristics of the beams.

The following recommendations are given for the linear accelerator for SBRT: Photon energies of 6 MV (or close to that) for tumors in the lungs. For tumors below the diaphragm (not passing through lung tissue), 6 to 20 MV. It is important to keep the treatment time reasonably short, preferably in the range of half an hour per target, as a maximum. The reason is mainly to avoid geometric errors from patient motion during a very long treatment time, but also to some extent to avoid a possible dose–rate effect. The following aspects are related to a short treatment time. A multileaf collimator (leaf width maximum 1 cm) should preferably be used to shape the beams, but customized blocks may be acceptable. The preferred dose rate should be at least 400 MU/min, but at least 250 MU/min can be acceptable Motorized wedges should preferably be used, but manual wedges may be acceptable. The size of the mechanical isocenter sphere should be within 1 mm in radius. Equipment (*e.g.*, lasers, video cameras, X-ray sources) in the treatment room used for setup should be accurately adjusted to the isocenter. The deviation of the actual isocenter point from the planned one should be aimed to be within 1 mm in the reference system defined by the fiducials (Figure). The mechanical sag on the treatment couch with the patient in treatment position and CT couch must be checked, and should be of the same order. This is of primary importance for targets extended in the cranial-caudal direction.

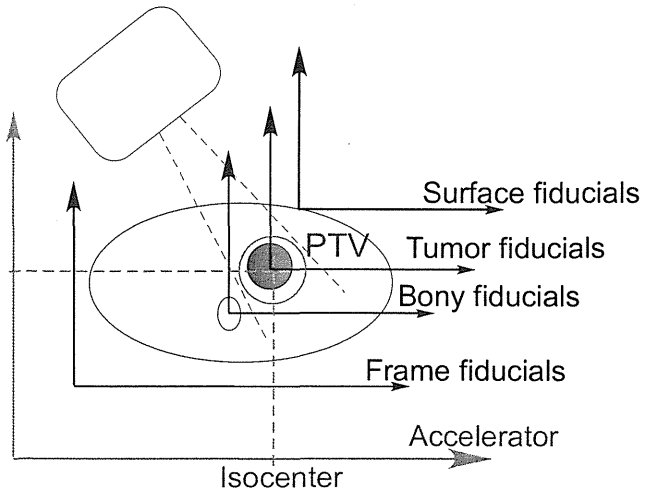

Fig. Patient treatment in the stereotactic body frame (ELEKTA Instr.). The correct isocenter position of the target and adequate suppression of breathing mobility by increased abdominal pressure is proved on the treatment couch by a mobile computed tomography device with gantry movements (Tomoscan M, Philips, Inc.).

Immobilization

Immobilization of the patient should be comfortable and also rigid to avoid intrafractional motions to ensure accurate repositioning of the patient between treatment planning and irradiation sessions. Both goals are usually achieved by tightly moulded vacuum pillows, which are attached to a stereotactic frame (e.g. SBF) or are used frameless (*e.g.,* Body-Fix). Specific attention should be directed to providing comfortable support for the arms and legs/knees, because they are most prone to become uncomfortable during a long treatment procedure (verification and irradiation might last up to 60 min).

Geometric verification

Geometric verification is a very important issue for SBRT because its single dose is usually more than 10 Gy and therefore constitutes 20–33% of the whole dose. A single misalignment will result in local failure or severe complication. The most simple verification method widely accepted is an anterior–posterior portal film taken before each session to compare with DRR (Digitally reconstructed radiographs) to check bony anatomy. EPID (Electronic portal imaging device) images can be used alternatively, but the sensitivity to detect setup error may be inferior to portal film. A more useful method is using the CT on rails. It is possible for CT images taken before and after SBRT to detect not only intertreatment setup error but intratreatment setup error. Recently, a couple of image-guided RT machines have been developed. With either the on-board or the in-room imaging apparatus, the position of a patient can be confirmed before every treatment day.

Target volumes and margins

Ideally, both gross tumor volume (GTV) and clinical target volume (CTV) should be geometrically defined in an unambiguous way in the reference system used. In clinical practice, however, there will always be some degree of breathing motion during imaging (even with gating there will be a residual motion) and differences in tumor position during imaging and treatment. ICRU 62 defines an internal margin (IM) and an internal target volume (ITV) for the physiologic movements and variations of the CTV during therapy. One way to get an estimate of the IM is to do the imaging during several breathing cycles (see Imaging for Planning, above). In the clinical practice of SBRT, ITV is not always defined explicitly, but PTV is usually drawn with standard margins to a CTV that has been defined by normal dose-planning imaging. The standard margins are determined from geometric verification imaging of patient cohorts and basically are valid only for the use of a particular set of conditions like patient fixation and breathing reduction, and also choice of reference system and method for setup and geometric verification. However, owing to similar geometric requirements using different methods for SBRT, a relatively narrow range of margins between CTV and PTV is currently used in clinical practice. With the immobilization equipment and methods for reduction of the target motion described in this report, the longitudinal margin is generally 10 mm. In the transverse plane, margins are usually 5 mm and up to 10 mm. Table 5 shows the margins used at different centers (16,18,19, 32,36,44,48–50,65,66).

Training requirements

The process of SBRT differs greatly from general RT in method and, more importantly, regarding patient selection, dose prescription/fractionation, target definition, and as a consequence toxicity patterns. Thus, training in SBRT is of major importance, and the following recommendations have been made: General methods for SBRT should be studied by RO (Radiation oncologist), medical physicist (MP), and radiation therapy technologist (RTT); patient selection criteria by RO; patient immobilization and accounting for internal organ motions by MP and RTT; imaging acquisition technique by MP and RTT; target definitions by RO; dose planning by MP; dose prescription by RO and MP; geometric verification by MP and RTT; treatment by RTT; toxicity patterns by RO; and follow-up by RO.

Personal experience is important not only in patient selection but also in proper use of the equipment, target definition, three-dimensional treatment planning, and follow-up of patients. Some vendors offer practical teaching courses with experienced faculty after the purchase of SBRT equipment.

QUALITY ASSURANCE REQUIREMENTS

General recommendations on quality assurance (QA) in RT also apply to SBRT. QA recommendations focused on SBRT have also been published (61), as have practice guidelines for the performance of SBRT (62). However, some aspects of QA that are of particular importance for SBRT are given below.

Table 5. Margins used for planning target volume definition for stereotactic body radiotherapy of different targets

Study	Organ	Margin transverse (mm)	Margin long (mm)	Comment	Method for breathing reduction
Timmerman *et al.*, (19)	Lung	5	10		Different methods
Bauman *et al.*, (66)	Lung	5, 10	10		Abd. comp
Zimmermann *et al.*, (65)	Lung	Individual	Individual		Abd. comp
Joyner *et al.*, (36)	Lung	5	10		
Okunieff (67)	Lung	7	10		Resp. gating
Paludan (68)	Lung	Minimum 5	10		Abd. comp
Hoyer *et al.*, (50)	Liver	Minimum 5*	10	*Later ind. margin	Abd. comp
Mendez-Romero *et al.*, (44)	Liver	5	10		Adom. comp
Wulf *et al.*, (16)	Liver	5	5, 10		Abd. comp
Kavanagh *et al.*, (48)	Liver	Minimum 5	10		Abd. comp or breath hold
Dawson *et al.*, (49)	Liver	Minimum 5*	min 5*	*Ind. margin	ABC
Svedman (69)	Liver, lung	5, 10	10		Abd. comp
Wurm (70)	Liver, lung	5	5		Adaptive gating
Hodge (71)	Lung	6	6*	*Margin to ITV	Abd. comp
Guckenberger (58)	Lung	5*	5*	*Margin to ITV	Abd. comp
Nagata *et al.*, (18)	Lung	5*	8–10*	*Margin to ITV	Abd. comp
Onishi *et al.*, (32)	Lung	0–5*	0–5*	*Margin to ITV	Different methods

Abbreviations: Resp. = respiratory; Abd. = abdominal compression. ABC = Automatic breezing control.

Treatment planning QA

Important aspects of treatment planning are adequate definitions of GTV, CTV, PTV, and OAR; conformity to dose requirements for target volumes; dose restrictions for OAR; practical aspects on a deliverable dose plan; isocenter coordinates; and accuracy in dose calculation.

The selection of adequate target volumes and an appropriate dose prescription are key factors in SBRT. Margins between GTV and CTV should be based on image information and clinical experience. The margin to PTV depends on the particular method used for SBRT, including the method for reducing internal target motion.

Evaluation of the conformity of the planned dose distribution to that intended is very important and generally requires a careful look-through of isodoses in the irradiated volume and also evaluation of dose–volume histogram data for the different volumes.

The practical aspects of the dose plan, in terms of the time for dose delivery and the possibility to reach the different beam directions, should be considered in the evaluation of the plan.

The accuracy of the dose calculation depends on the particular dose calculation algorithm used in the treatment planning system (59) and on the quantity and quality of the input data used for modeling the particular beam (radiation quality). It is important that the modeling of beam data accurately describes the beam profiles, especially with regard to geometry in the penumbra region.

Setup and geometric verification QA

The QA aspects of the geometric dose delivery are of great importance in SBRT. This can be divided into aspects of setup and geometric verification. Of importance for setup at the accelerator is that procedures for patient positioning on the treatment unit couch are the same as on the CT. Procedures to assure that the correct isocenter coordinates are used should be implemented. Preferably, this can be done with double-checking. Lasers, video cameras, imaging devices, or other equipment used for setup must be accurately aligned to the coordinate system of the accelerator (usually the mechanical isocenter (Figure). This should be checked with a phantom. The mechanical isocenter should also be checked periodically and preferably be within 0.5 mm in radius.

An important characteristic of SBRT is that direct geometric verification of the target image is used instead of imaging of surrogates for the target position, as in conventional RT. Today, several different geometric imaging methods are used in SBRT. These are CT on a device separate from the treatment unit, CT (with slit-beam or cone-beam) on a device built into the treatment unit, and projection imaging of gold markers in the tumor or of a bony tumor. For all these methods, procedures must be implemented to ensure that a proper image registration method is used to align the reference system in the geometric verification images with the same reference system in the reference image set. This procedure should be based on imaging of a phantom.

ECONOMIC CONSIDERATIONS

From the economic perspective, SBRT is more cost beneficial than surgery. In 2004, SBRT for lung tumor and liver tumors was approved by the government for insurance coverage in Japan. The charge for SBRT is only 630,000 Yen. By contrast, the surgical fee for lobectomy is approximately 900,000 Yen. The surgical fee for video-assisted thoracoscopic surgery requires both surgical and instrumental fees of 960,000 to 980,000 Yen. Other costs

including hospital charges and drug fees are higher for surgical and video-assisted thoracic surgery cases than for SBRT cases. Although similar cost comparisons for treatment in the United States and Europe have not been reported, to our knowledge, it follows that similar differences would be seen as in Japan.

SUMMARIES AND RECOMMENDATIONS

Accumulated evidence coming from the developed world strongly favors SBRT for various lung and other body tumors as an effective treatment option with acceptable toxicity (63, 64). It is expected that ongoing clinical trials will further refine its approach in selected populations of patients who are not surgical candidates for various reasons. In particular, it seems that the absolute indication of SBRT is the inoperable patient with peripheral histologically confirmed T1–3N0M0 (<5 cm) lung cancer.

However, in practice, other indicators for SBRT are encountered. Examples are an elderly patient with peripheral histologically confirmed T1–3 N0M0 (<5 cm) lung cancer who declines surgery; a patient with peripheral histologically unconfirmed (<5 cm) but radiologically diagnosed lung tumor who also declines surgery; or a patient with oligometastatic lung cancer. Other patients with primary liver cancer, oligometastatic liver cancer, pancreatic cancer, and kidney cancer could be candidates for SBRT when clinically applicable. Finally, when the patient who does not want surgery has been considered operable, SBRT can be an alternative choice.

These recommendations apply for both developed and developing countries. Moreover, several advantages inherent in the latter, such as preferred short treatment courses, fewer hospitalizations, and transport to and from hospitals, all make the cost effectiveness of this method favorable. However, certain disadvantages also exist, including high capital costs, lack of supporting (pretreatment and treatment) services, and, regardless of region, fewer patients than are usually seen in the developed world. Despite the latter, SBRT has recently been introduced in several developing countries with adequate logistics and infrastructure, which constitutes an important step toward the improvement of RT results that has been awaited for many years.

REFERENCES

1. Kanavos P. The rising burden of cancer in the developing world. *Ann Oncol* 2006;17(Suppl 8):15–23.
2. Sener SF, Grey N. The global burden of cancer. *J Surg Oncol* 2005;92:1–3.
3. World Health Organisation. National cancer control programs: Policies and managerial guidelines. Geneva, Switzerland: WHO; 2002.
4. Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol* 2006;7:584–595.
5. Ramondetta LM, Sun C, Hollier L, *et al.* Advanced cervical cancer treatment in Harris County: Pilot evaluation of factors that prevent optimal therapy. *Gynecol Oncol* 2006;103: 547–553.
6. Plataniotis GA, Kouvaris JR, Dardoufas C, *et al.* A short radiotherapy course for locally advanced non-small cell lung cancer (NSCLC): Effective palliation and patients' convenience. *Lung Cancer* 2002;35:203–207.
7. Levin CV, El Gueddari B, Meghzifene A. Radiation therapy in Africa: Distribution and equipment. *Radiother Oncol* 1999;52: 79–84.
8. Tatsuzaki H, Levin CV. Quantitative status of resources for radiation therapy in Asia and Pacific region. *Radiother Oncol* 2001;60:81–89.
9. Zubizarreta EH, Poitevin A, Levin CV. Overview of radiotherapy resources in Latin America: A survey by the International Atomic Energy Agency (IAEA). *Radiother Oncol* 2004;73:97–100.
10. The Radiation Oncology Inquiry. A vision for radiotherapy. Canberra: Commonwealth of Australia; 2002.
11. Lax I, Blomgren H, Näslund I, *et al.* Stereotactic radiotherapy of malignancies in the abdomen: Methodological aspects. *Acta Oncol* 1994;33:677–683.
12. Lax I, Blomgren H, Larson D, *et al.* Extracranial stereotactic radiosurgery of localized targets. *J Radiosurg* 1998;1:135–148.
13. Timmerman R, Galvin J, Michalski J, *et al.* Accrediation and quality assurance for Radiation Oncology Group: Multicenter clinical trials using stereotactic body radiation therapy in lung cancer. *Acta Oncol* 2006;45:779–786.
14. ICRU 62: Prescription, recording and reporting photon beam therapy. Bethesda: ICRU; 1999.
15. Uematsu M, Yamamoto F, Takai K, *et al.* Stereotactic radiation therapy for primary or metastatic lung cancer: Preliminary experience with a linear accelerator-based treatment unit. *Int J Radiat Oncol Biol Phys* 1996;36(Suppl):352.
16. Wulf J, Haedinger U, Oppitz U, *et al.* Stereotactic radiotherapy of targets in the lung and liver. *Strahlenther Onkol* 2001;177: 645–655.
17. Herfarth KK, Debus J, Lohr F, *et al.* Stereotactic single dose radiation therapy of liver tumors: Results of a phase I/II trial. *J Clin Oncol* 2001;19:164–170.
18. Nagata Y, Negoro Y, Aoki T, *et al.* Clinical outcomes of 3D conformal hypofractionated single high dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2002;52:1041–1046.
19. Timmerman R, Papiez L, McGarry R, *et al.* Extracranial stereotactic radioablation: Results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003;124: 1946–1955.
20. Blomgren H, Lax I, Näslund I, *et al.* Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. *Acta Oncol* 1995;34:861–870.
21. Uematsu M, Shioda A, Tahara K, *et al.* Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients. *Cancer* 1998;82:1062–1070.
22. Shirato H, Shimizu S, Tadashi S, *et al.* Real time tumor tracking radiotherapy. *Lancet* 1999;353:1331–1332.
23. Uematsu M, Shioda M, Suda A, *et al.* Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: A 5-year experience. *Int J Radiat Oncol Biol Phys* 2001;51:666–670.
24. Arimoto T, Usubuchi H, Matsuzawa T, *et al.* Small volume multiple non-coplanar arc radiotherapy for tumors of the lung, head & neck and the abdominopelvic region. Tokyo: Elsevier; 1998.
25. Onimaru R, Shirato H, Shimizu S, *et al.* Tolerance of organs at risk in small-volume, hypofractionated, image-guided

radiotherapy for primary and metastatic lung cancers. *Int J Radiat Oncol Biol Phys* 2003;56:126–135.
26. Wulf J, Haedinger U, Oppitz U, *et al.* Stereotactic radiotherapy of primary lung cancer and pulmonary metastases: A non-invasive treatment approach in medically inoperable patients. *Int J Radiat Oncol Biol Phys* 2004;60:186–196.
27. Lee S, Choi E, Park H, *et al.* Stereotactic body frame based fractionated radiosurgery on consecutive days for primary or metastatic tumors in the lung. *Lung Cancer* 2003;40: 309–315.
28. Nagata Y, Takayama K, Matsuo Y, *et al.* Clinical outcomes of a phase I/II of 48Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005;63:1427–1431.
29. Fakiris A, McGarry RC, Yiannoustsons CT, *et al.* Stereotactic body radiation therapy for early-stage non-small cell lung carcinoma: Four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677–682.
30. Baumann P, Nyman J, Hoyer M, *et al.* Outcome in a prospective phase II trial of medically inoperable stage I non-small cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290–3296.
31. Timmermann R, Paulus R, Galvin J, *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–1076.
32. Onishi H, Araki T, Shirato H, *et al.* Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma. *Cancer* 2004;101:1623–1631.
33. Nagata Y, Matsuo Y, Takayama K, *et al.* Survey of SBRT in Japan. *Int J Radiat Oncol Biol Phys* 2009;75:343–347.
34. Timmerman R, McGarry R, Yiannoutsos C, *et al.* Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24: 4833–4839.
35. Chang JY, Balter PA, Dong L, *et al.* Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;72:967–971.
36. Joyner M, Salter BJ, Papanikolaou N, *et al.* Stereotactic body radiation therapy for centrally located lung tumors. *Acta Oncol* 2006;45:802–807.
37. Wulf J, Baier K, Mueller G, *et al.* Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol* 2005;77: 83–87.
38. Hara R, Itami J, Kondo T, *et al.* Clinical outcomes of single-fraction radiation therapy for lung tumors. *Cancer* 2006; 1006:1347–1352.
39. Kavanagh BD, McGarry R, Timmerman RD. Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastases. *Semin Radiat Oncol* 2006;16:77–84.
40. Norihisa Y, Nagata Y, Takayama K, *et al.* Stereotactic body radiation therapy for oligometastatic lung tumors. *Int J Radiat Oncol Biol Phys* 2008;72:398–403.
41. Rusthoven KE, Kavanagh BD, Burri SH, *et al.* Multi-institutional phase I/II trial of stereotactic radiation therapy for lung metastases. *J Clin Oncol* 2009;27:1579–1584.
42. Lehnert T, Golling M. Indikationen und Ergebnisse der Lebermetastasenresektion. *Radiologe* 2001;41:40–48.
43. Blomgren H, Lax I, Göranson H, *et al.* Radiosurgery for tumors in the body: Clinical experience using a new method. *J Radiosurgery* 1998;1:63–74.
44. Mendez-Romero A, Wunderink W, Hussain S, *et al.* Stereotactic body radiation therapy for primary and metastatic liver tumors: A single-institution phase I-II study. *Acta Oncol* 2006; 45:831–837.
45. Herfarth KK, Debus J. Stereotaktische Strahlentherapie von Lebermetastasen. *Der Chirurg* 2005;76:564–569.
46. Wulf J, Guckenberger M, Haedinger U, *et al.* Stereotactic radiotherapy of primary liver cancer and hepatic metastases. *Acta Oncol* 2006;45:838–847.
47. Schefter T, Kavanagh B, Timmerman R, *et al.* A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int J Radiat Oncol Biol Phys* 2005;62:1371–1378.
48. Kavanagh B, Schefter T, Cardenes H, *et al.* Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. *Acta Oncol* 2006;45:848–855.
49. Dawson L, Eccles C, Craig T. Individualized image guided iso-NTCP based liver cancer SBRT. *Acta Oncol* 2006;45:856–864.
50. Hoyer M, Roed H, Sengelov L, *et al.* Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol* 2005;76:48–53.
51. Koong AC, Le Q, Ho A, *et al.* Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1017–1021.
52. Koong AC, Christofferson E, Le Q, *et al.* Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005; 63:320–323.
53. Wersaell P, Blomgren H, Lax I, *et al.* Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. *Radiother Oncol* 2005;77:88–95.
54. Takayama K, Nagata Y, Negoro Y, *et al.* Treatment planning of stereotactic radiotherapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:1565–1571.
55. Yaes RJ, Patel P, Maruyama Y. On using the linear-quadratic model in daily clinical practice. *Int J Radiat Oncol Biol Phys* 1991;20:1353–1362.
56. Timmerman RD, Park C, Kavanagh BD. The North American experience with stereotactic body radiation therapy in non-small cell lung cancer. *J Thorac Oncol* 2007;27(Suppl3): S101–S112, Appendix.
57. Laagerward F, Van Sornsen de Koste J, Nijssen-Visser M, *et al.* Multiple "slow" CT scans for incorporating lung tumor mobility in radiotherapy planning. *Int J Radiat Oncol Biol Phys* 2001;51:932–937.
58. Guckenberger M, Meyer J, Wilbert J, *et al.* Intra-fractional uncertainties in cone-beam CT based image-guided radiotherapy of pulmonary tumors. *Radiother Oncol* 2007;83: 57–64.
59. Pannetieri V, Wennberg B, Gagliardi G, *et al.* SBRT of lung tumors: Monte Carlo simulation with PENELOPE of dose distributions including respiratory motion and comparison with different treatment planning systems. *Phys Med Biol* 2007; 52:4265–4281.
60. Lax I, Panettieri V, Wennberg B, *et al.* Dose distributions in SBRT of lung tumors: Comparison between two different treatment planning algorithms and Monte-Carlo simulation including breathing motions. *Acta Oncol* 2006;45:978–988.
61. Haedinger U, Wulf J. Quality assurance in stereotactic body radiation therapy. In: Kavanagh BD, Timmerman R, editors. Stereotactic body radiation therapy. Philadelphia: Lippincott, Williams & Wilkins; 2005.
62. Potter L, Steinberg M, Rose C, *et al.* American Society of Therapeutic Radiology and Oncology and American College of Radiology practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2004; 60:1026–1032.
63. Xia T, Li H, Sun Q, *et al.* Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable stage I/II non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;66:117–125.

64. McGarry R, Papiez L, Williams M, *et al.* Stereotactic body radiation therapy for early stage non-small cell lung cancer: Phase I study. *Int J Radiat Oncol Biol Phys* 2005;63:1010–1015.
65. Zimmermann F, Geinitz H, Schill S, *et al.* Stereotactic hypofractionated radiation therapy for stage I non-small cell lung cancer. *Lung Cancer* 2005;48:107–114.
66. Baumann P, Nyman J, Lax I, *et al.* Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer:A retrospective analysis of patients treated in the Nordic courntries. *Acta Oncol* 2006;45:787–795.
67. Okunieff P, Petersen AL, Philip A, *et al.* Stereotactic body radiationtherapy for lung metastases. *Acta Oncol* 2006;45: 808–817.
68. Pauldan M, Traberg HA, Petersen J, *et al.* Aggravation of dyspnea in stage I non-small cell lung cancer patient following stereotactic bosy radiotherapy: Is there a dose-response dependency? *Acta Oncol* 2006;45:818–822.
69. Svedman C, Karlsson K, Rutkowska E, *et al.* Stereotactic bosy radiotherapy of primary and metastatic renal lesions for patients with one functioning kidney. *Acta Oncol* 2008;47: 1578–1583.
70. Wurm RE, Gum F, Erbel S. Iimage guided respiratory gated hypofractionated stereotactic body radiation therapy (H-SBRT) for liver and lung tumors. Initial experience. *Acta Oncol* 2006;45:881–889.
71. Hodge W, Tome WA, Jaradat HA, *et al.* Feasibility report of image guided stereotactic body radiation therapy (IG-SBRT) with tomotherapy for early stage medically inoperable lung cancerusing extreme hypofractionation. *Acta Oncol* 2006;45: 890–896.

J Hepatobiliary Pancreat Sci (2013) 20:538–544
DOI 10.1007/s00534-013-0596-0

ORIGINAL ARTICLE

Risk factor analysis and prevention of postoperative pancreatic fistula after distal pancreatectomy with stapler use

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Published online: 22 February 2013
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Abstract
Background Postoperative pancreatic fistula (POPF) is a major, intractable complication after distal pancreatectomy (DP). Risk factor evaluation and prevention of this complication are important tasks for pancreatic surgeons.
Methods One hundred and six patients who underwent DP using a stapler for pancreatic division were retrospectively investigated. The relationship between clinicopathological factors and the incidence of POPF was statistically analyzed.
Results Clinically relevant, Grade B or C POPF by International Study Group of Pancreatic Fistula criteria occurred in 52 patients (49.1 %). Age, American Society of Anesthesiologists score, body mass index, and concomitant gastrointestinal tract resection did not influence the incidence of POPF. Use of a double-row stapler and a thick pancreatic stump were significant risk factors for POPF in multivariate analysis. Compression index was also shown to be an important factor in cases in which the pancreas was divided by a stapler.
Conclusions The most important risk factor for POPF after DP was suggested to be the thickness of the pancreatic stump, reflecting the volume of remnant pancreas. A triple-row stapler seemed to be superior to a double-row stapler in preventing POPF. However, triple-row stapler use in a thick pancreas is considered to be a future problem to be solved.

Keywords Distal pancreatectomy · Pancreatic fistula · Stapler · Pancreatic thickness · Compression index

Introduction

Although operative management and techniques in pancreatic surgery have progressed in the last several decades, postoperative pancreatic fistula (POPF) remains a devastating complication, because it is intractable, needs prolonged drain insertion, and can lead to further morbidity and mortality. It is generally reported that the incidence of POPF after distal pancreatectomy (DP) is 5–40 % following the establishment of the International Study Group of Pancreatic Fistula (ISGPF) criteria [1–4]. Various reports have discussed the risk factors for POPF after DP, and surgical techniques for pancreatic division have been attempted to prevent POPF, but promising management still does not exist [2, 4–13]. The DISPACT study, a recent large randomized controlled trial that examined the efficacy of stapler versus hand-sewn closure, showed that stapler closure did not reduce the rate of POPF, with a POPF rate of 32 % in the stapler group and 28 % in the hand-sewn group [14]. A recent meta-analysis also showed

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a similar risk of POPF occurrence, with 22.1 % in the stapler group and 31.2 % in the suture group [3]. The risk factors and prevention of POPF after DP seem to depend on the technique of division and closure of the pancreatic remnant, unless coverage or anastomosis to the stump is established. Dividing the pancreas by stapler is still common because of convenience, with advances in the devices for the field of abdominal surgery, and will continue to be required because of the wider indication for endoscopic surgery. Few reports have been published on whether the type of stapler, double-row or triple-row, influences POPF after DP. This study examined risk factors that may be associated with the occurrence of POPF after DP using a stapler for division of the pancreas, and analyzed the impact of the type of stapler.

Methods

Patients and clinical data collection

One hundred and forty consecutive patients who underwent DP at the National Cancer Center Hospital East between August 2006 and December 2011 were retrospectively investigated. Clinicopathological data were reviewed from the medical records. Twenty-one patients who underwent insertion of an open drain intraoperatively and 13 patients who underwent pancreatic resection, not with a stapler but with laparosonic coagulating shears (LCS) or knife, were excluded. An open drain was considered to be a risk for retrograde intra-abdominal infection, which is related to the risk of POPF, as we reported in a previous study [15]. Patient characteristics are shown in Table 1. The study was approved by the institutional review board of the National Cancer Center.

Operative techniques

After dissection of the peripancreatic space, ligation of the splenic artery and vein, and lymphadenectomy as needed, the pancreas was divided by one of the following techniques: double-row stapler (Proximate reloadable stapler, TLH 60; Ethicon Endo-Surgery, Cincinnati, OH, USA) with LCS or knife, or triple-row stapler (Echelon 60 mm; Ethicon Endo-Surgery, GIA Universal or Endo-GIA Ultra tri staple 60 mm; Covidien, North Haven, CT, USA). The resection site was usually above the portal vein–superior mesenteric vein (PV-SMV) axis, preserving an adequate surgical margin. The type of stapler was selected at the surgeon's discretion as well as based on changing trends. The cartridge height of the stapler was selected according to the pancreatic texture or thickness by rough intraoperative estimation. Main pancreatic duct (MPD) ligation or absorbable polyglycolic acid reinforcement felt was used for division using a double-row stapler as an additional technique in particular cases.

Gastrointestinal (GI) tract resection was performed in cases in which there appeared to be invasion by pancreatic cancer or in which it was difficult to dissect and preserve intestines, or that harbored gastric cancer. All patients underwent placement of two closed suction drains, one at the pancreatic stump and the other in the left subphrenic space. Operative data are shown in Table 2.

Perioperative management

Drainage data of amylase level (D-Amy, IU/ml) and culture results were evaluated on postoperative day (POD) 1, 3, 5, and 7. An oral diet was restarted on POD4 in general, regardless of whether POPF existed or not. A first generation cefem was used for perioperative antibiotic

Table 1 Patient characteristics

	POPF Grade B/C (n = 52)	None or POPF Grade A (n = 54)
Age (years)	61.9 ± 13.8	65.4 ± 11.9
Sex (male)	36 (69.2 %)	33 (61.1 %)
BMI (kg/m^2)	22.2 ± 3.4	21.0 ± 2.9
ASA score (1/2/3/4)	14/35/5	23/25/4
Preoperative serum albumin (mg/dl)	4.0 ± 0.5	4.0 ± 0.5
Diabetes	11 (21.2 %)	13 (24.1 %)
Smoking history	29 (55.8 %)	22 (40.7 %)
Neoadjuvant chemotherapy	0 (0.0 %)	3 (5.6 %)
Histopathological diagnosis		
Malignant disease	46 (88.5 %)	51 (94.4 %)
Pancreatic cancer	31 (59.6 %)	35 (64.8 %)
Gastric cancer	13 (25.0 %)	14 (25.9 %)
Metastatic disease	2 (3.8 %)	2 (3.7 %)
Benign disease	6 (11.5 %)	3 (5.6 %)

POPF postoperative pancreatic fistula, *BMI* body mass index, *ASA* American Society of Anesthesiologists

Table 2 Operative factors

	POPF Grade B/C ($n = 52$)	None or POPF Grade A ($n = 54$)
DP		
+Splenectomy	50 (96.2 %)	52 (96.3 %)
+GI tract resection	17 (32.7 %)	20 (37.0 %)
Gastrectomy	15 (28.8 %)	19 (35.2 %)
Jejunal resection	2 (3.8 %)	3 (5.6 %)
Colectomy	4 (7.7 %)	1 (1.9 %)
+SMA perineural dissection	12 (23.1 %)	13 (24.1 %)
+PV resection	1 (1.9 %)	1 (1.9 %)
+Celiac axis resection	3 (5.8 %)	1 (1.9 %)
+Para-aortic lymph node dissection	3 (5.8 %)	0 (0.0 %)
Type of stapler (double-row/triple-row)	47/5	40/14
Pancreatic resection site: near above PV-SMV	37 (71.2 %)	39 (72.2 %)
Additional MPD ligation after pancreatic resection	5 (9.6 %)	8 (14.8 %)
Absorbable PGA reinforcement felt use	10 (19.2 %)	8 (14.8 %)
Operation time (min)	224 ± 74	222 ± 82
Blood loss (ml)	632 ± 415	675 ± 887

POPF postoperative pancreatic fistula, *DP* distal pancreatectomy, *GI* gastrointestinal, *SMA* superior mesenteric artery, *PV* portal vein, *SMV* superior mesenteric vein, *MPD* main pancreatic duct, *PGA* polyglycolic acid

prophylaxis. Somatostatin analogues were never administered perioperatively in an attempt to prevent or treat POPF. Drains were removed when the drainage fluid did not show extremely high D-Amy or sign of infection after POD5. Drain replacement via the ordinary tract created at operation was performed under fluorography on POD7–14, in order to prevent drain occlusion and achieve effective drainage in cases that showed signs of infection in the drainage fluid.

Pancreatic factors

The configuration of the pancreatic stump was evaluated in detail. Thickness, width, and main pancreatic duct diameter (MPDd) were defined as shown in Fig. 1. The pancreatic parenchyma was considered to be the difference between the whole pancreatic stump and MPD. Each parameter was calculated on the assumption that the pancreas was an ellipse, and the MPD a circle. The pancreatic resection site was reviewed, and these parameters were measured using 2-mm-slice high-resolution multi-detector CT. Compression index was defined as the ratio of stapler height at closure to stump thickness.

Definitions of POPF

POPF was basically diagnosed according to the ISGPF criteria: Grade A: transient fistula with no clinical effect, with D-Amy greater than 3 times the upper normal serum value on or after POD3; Grade B: requiring change in management (e.g. drain replacement with prolonged drain insertion); Grade C: requiring major change in clinical management (clinical stability may be borderline and more aggressive intervention needed, e.g., intra-abdominal hemorrhage). The POPF cases in this study were considered to be "clinically relevant", consistent with Grade B or C of the ISGPF criteria.

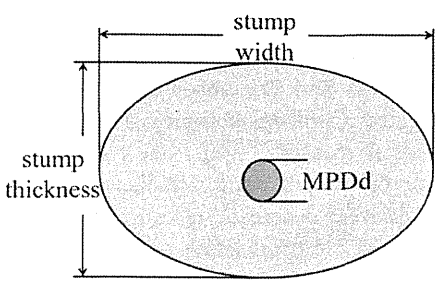

Fig. 1 Configuration of the pancreatic stump. MPDd (mm): main pancreatic duct diameter; parenchymal thickness (mm): stump thickness – MPDd; MPD area (mm^2): 1/4 × MPDd × MPDd × π; stump area (mm^2): 1/4 × stump width × stump thickness × π; parenchymal area (mm^2): stump area – MPD area

Statistical analysis

Patient characteristics, operative factors, and pancreatic measurements were compared between patients who did and did not experience "clinically relevant" POPF. Pancreatic measurements were compared using the Mann–Whitney *U* test to screen out covariates that could be associated with POPF. Categorical variables are summarized as numbers and percentages, and continuous variables are presented as mean ± SD.

Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors for POPF. Covariates known to be risk factors for POPF were included [4, 16–21]. Furthermore, we evaluated whether the compression index would change the result of regression analyses, by substituting it for stump thickness. All statistical analyses were performed using SAS Release 9.3 (SAS Institute, Inc., Cary, NC, USA). All P values were based on two-sided statistical tests, setting the significance level as 0.05.

Results

Fifty-two patients (49.1 %) had "clinically relevant" POPF, which corresponded to Grade B of the ISGPF definition. No patient with Grade C was identified. Grade A was observed in 24 patients. There were 6 patients with wound infection, 3 with pneumonia, and 4 with delayed gastric emptying.

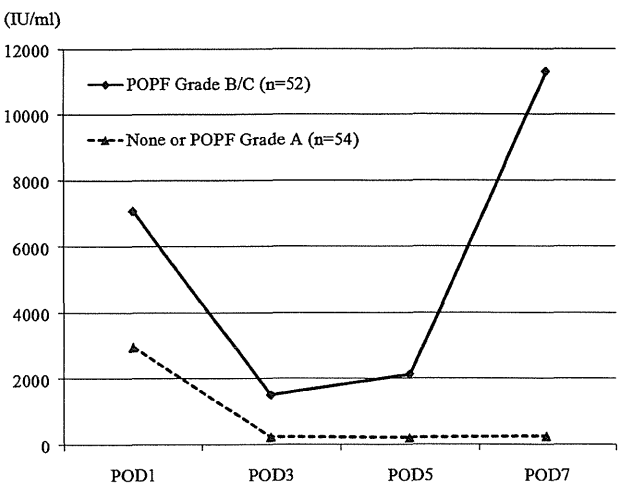

Fig. 2 Relationship between drainage data of amylase level (D-Amy) on each postoperative day (POD) and POPF D-Amy in the POPF Grade B/C group on POD1, 3, 5, and 7. There was a gradual decreased in the None or POPF Grade A group, but a gradual increased in the POPF Grade B/C group

Drainage data

Figure 2 shows the drainage data of both groups. D-Amy in the POPF Grade B/C group was significantly higher than that in the None or POPF Grade A group on POD1, 3, 5, and 7. It decreased gradually in the None or POPF Grade A group, while it gradually increased in the POPF Grade B/C group.

Pancreatic measurements

The correlation between pancreatic stump measurement data and clinically relevant POPF is shown in Table 3. Parenchymal thickness was the most significant factor in the POPF Grade B/C group, followed by parenchymal area, stump thickness, and stump area. Of these, stump thickness was representatively used in multivariate analyses.

Multivariate analyses for risk factors for clinically relevant POPF

As shown in Table 4, double-row stapler use and stump thickness were significant risk factors for POPF Grade B/C. Age, ASA score, body mass index (BMI), and concomitant GI tract resection were not significant in both univariate and multivariate analyses. The results of ancillary multivariate analysis are shown in Table 5, which substituted the compression index for the stump thickness. In spite of the missing data of compression index, double-row stapler use and compression index were significant risk factors for POPF Grade B/C.

Table 3 Pancreatic measurements

	POPF Grade B/C (n = 52)	None or POPF Grade A (n = 54)	P
MPDd (mm)	2.0 ± 0.7	2.7 ± 2.2	0.284
Stump thickness (mm)	12.9 ± 3.8	11.1 ± 3.4	0.017*
Stump width (mm)	31.0 ± 7.6	12.5 ± 8.7	0.273
Parenchymal thickness (mm)	10.9 ± 3.9	8.3 ± 3.6	0.001*
Stump area (mm^2)	322.3 ± 144.8	257.5 ± 107.4	0.025*
MPD area (mm^2)	3.6 ± 2.6	9.6 ± 21.0	0.284
Parenchymal area (mm^2)	318.7 ± 145.2	247.9 ± 103.0	0.012*
Compression index[a]	0.19 ± 0.08	0.16 ± 0.06	0.029*

POPF postoperative pancreatic fistula, *MPD* main pancreatic duct, *MPDd* main pancreatic duct diameter

* $P < 0.05$

[a] Compression index was defined as the ratio of stapler height at closure to stump thickness

Table 4 Analysis of risk factors for POPF Grade B/C ($n = 106$)

	Univariate analysis	Multivariate analysis		
	P	Odds ratio	95 % CI	*P*
Age ≥65 (years)	0.448	0.97	0.39–2.44	0.951
ASA score 2 or 3	0.050	0.51	0.20–1.33	0.168
BMI ≥25 (kg/m^2)	0.341	2.11	0.53–8.33	0.287
Concomitant GI tract resection	0.639	0.86	0.35–2.15	0.755
Double-row stapler	0.035*	3.85	1.19–12.50	0.024*
Stump thickness	0.012*	1.14	1.01–1.28	0.032*

POPF postoperative pancreatic fistula, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *GI* gastrointestinal

* $P < 0.05$

Table 5 Analysis of risk factors for POPF Grade B/C including "compression index" instead of stump thickness ($n = 85$)

	Univariate analysis	Multivariate analysis		
	P	Odds ratio	95 % CI	*P*
Age ≥65 (years)	0.448	0.96	0.39–2.44	0.931
ASA score 2 or 3	0.050	0.46	0.20–1.33	0.146
BMI ≥25 (kg/m^2)	0.341	1.78	0.53–8.33	0.456
Concomitant GI tract resection	0.639	0.81	0.35–2.15	0.692
Double-row stapler	0.035*	3.85	1.19–12.50	0.032*
Compression index[a]	0.029*	5.00	1.28–20.00	0.020*

POPF postoperative pancreatic fistula, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *GI* gastrointestinal

* $P < 0.05$

[a] Compression index was defined as the ratio of stapler height at closure to stump thickness

Discussion

The incidence of clinically relevant POPF after DP in this study was relatively high compared with previous reports [1–4]. There are various considerations in the interpretation of POPF, even after the establishment of the ISGPF criteria. POPF is typically confirmed in cases in which the drainage fluid shows a so-called wine red color, high D-Amy, and subsequent signs of infection of characteristic partially granular and purulent fluid as a result of saponification. However, it is sometimes difficult to make the clinical judgment of whether to carry out prolonged drain insertion to drain septic fluid, in particular in cases where it is difficult to distinguish POPF from other infective conditions. Controversial cases, for example, those without a markedly high D-Amy but requiring drain replacement because of subtle signs of infection, were included in POPF Grade B in this study, because intra-abdominal abscess drainage from a drain inserted near the pancreatic stump could be assumed to be due to POPF, unless another apparent cause of drain infection were detected. Of 52 Grade B cases, 8 did not show even ISGPF Grade A findings on POD 3 but were considered to be Grade B during the entire clinical course. To elucidate whether the preceding origin was pancreatic leakage or intra-abdominal infection is occasionally difficult. Patients who underwent GI tract resection did not show a significantly higher incidence of POPF, which suggests that possible contamination due to GI tract resection did not influence POPF.

In the drainage data, median D-Amy decreased in both groups during POD1–3, although D-Amy in the POPF Grade B/C group remained high and increased significantly even after POD5 (Fig. 2). The mechanism of clinically problematic POPF after DP was hypothesized to be that retrograde drain infection occurred subsequently in the situation of amylase-rich fluid collection, which could easily give rise to tissue injury or decrease host resistance, local anti-inflammatory factors, and the nutritional state. Although drain insertion might be necessary for only a few early postoperative days, in order to prevent dispersion of amylase-rich pancreatic juice from the stump and to allow the diagnosis of POPF after DP, the drain should be removed as early as possible, in consideration of wound healing and retrograde infection. The most important point in reducing the incidence of POPF is to close the entire pancreatic stump completely at operation.

Risk factors for clinically relevant POPF after DP have been reported in many papers. Male sex, younger age, high BMI, diabetes, large volume of pancreatic remnant, longer operation time, additional procedures, extended lymphadenectomy, and staple size of 4.1 mm were previously reported to be associated with higher risk [4, 16–21].