Table 3 Summary of local control after stereotactic body radiotherapy for liver tumor

First author	Ref.	Target	Year	Case no.	Total RT dose	Fr no.	LC	Timing of LC
Blomgren H	[30]	HCC	1995	20	15-45 Gy	1-5	80%	1.5-38 mo
Tse RV	[26]	HCC & IHC	2008	41	36 Gy	6	65%	12 mo
Cardenes HR	[31]	HCC	2010	17	36-48 Gy	3	100%	10-42 mo
Kwon JH	[32]	HCC	2010	42	30-39 Gy	3	68%	36 mo
Louis C	[33]	HCC	2010	25	45 Gy	3	95%	24 mo
Seo YS	[34]	HCC	2010	38	33-57 Gy	3-4	66%	24 mo
Andolino DL	[28]	HCC	2011	60	40 Gy, 44 Gy	5	90%	24 mo
						3		
Kang JK	[29]	HCC	2012	50	42-60 Gy	3	95%	24 mo
Takeda A	[21]	HCC	2013	63	35-40 Gy	5	92%	36 mo
Herfarth KK	[10]	ML	2001	37	14-26 Gy	*NA*	78%	5.7 mo
Wada H	[11]	ML	2004	34	45 Gy	3	86%	12 mo
Kavanagh BD	[12]	ML	2006	36	60 Gy	3	93%	18 mo
Hoyer M	[13]	ML	2006	64	45 Gy	3	63%	24 mo
Katz AW	[14]	ML	2007	69	30-55 Gy	*NA*	57%	20 mo
Lee MT	[16]	ML	2009	68	27.7-60 Gy	6	71%	12 mo
Rusthoven KE	[17]	ML	2009	47	36-60 Gy	3	92%	24 mo
Rule W	[18]	ML	2011	27	30 Gy,	3	56%	24 mo
					50 Gy,	5	89%	
					60 Gy	5	100%	
Chang DT	[19]	ML	2011	65	46-52 Gy	3	90%	12 mo
Fumagalli I	[20]	ML	2012	90	15 Gy	3	66%	24 mo

Abberiviation: HCC hepatocellular carcinoma, *IHC* intrahepatic cholangiocarcinoma, *ML* metastatic liver tumor, *RT* radiotherapy, Fr = fractions, LC = local control, *mo* months.

LCR might be overestimated using cumulative LCR like the present report because patients who died without the evidence of local recurrence were excluded. Since the pure LCR want to be calculated, the patients who died without local recurrence were treated as a censored case. Takeda *et al.* [21] reported that LCR after SBRT for lung metastases from colorectal cancer with a 2-year LCR of 72% was worse than that for primary lung cancer and also in the present study, LCR for liver metastases from colorectal cancer was slightly worse than that for HCC or liver metastases from other cancers, although there was no significant difference. The patient number at this time may be too small to detect the significant differences on LCR among three groups.

To improve our results of local control and so on, we may increase radiation dose. The median BED_{10} in this study was 96 Gy for patients with HCC and 106 Gy with metastatic liver tumor. Although it is natural that BED_{10} is over 100 Gy in the SBRT for lung tumor, the fact may be not true of the SBRT for liver tumor. Although the aim of SBRT is to deliver a high ablative dose to destroy tumor cells, the optimal treatment dose should be determined based on both tumor control and long-term safety because radiation damage to the normal liver tissue is dose-volume-dependent [35,36]. In SBRT for liver tumors, the prescribed dose and fraction vary across studies, ranging from 24–60 Gy in 2–6 fractions, and most studies focused predominantly on liver metastases [37]. Since metastatic lung tumors require dose escalation due to relatively low radio-sensitivity [38], increasing the dose to metastatic liver tumors appears to be reasonable, and patients with normal liver function treated with SBRT have rarely developed RILD. In contrast, dose escalation in HCC patients with decompensated cirrhotic liver disease may be disadvantageous with respect to normal liver tolerance. A dose-control relationship has been described for patients treated with SBRT for liver and lung metastases. In an analysis of 246 lesions treated with three-fraction SBRT for primary or metastatic tumors within the lung or liver, McCammon *et al.* [39] demonstrated significant improvement in local control with increasing dose and the 3-year local control rate in their series was 89.3% for those lesions that received 54 to 60 Gy versus 59% and 8.1% for lesions that received 36 to 53.9 Gy and less than 36 Gy, respectively ($p < 0.01$). Tekeda *et al.* [40] used 35–40 Gy in 5 fractions based on baseline liver function and liver

volume receiving ≥20 Gy of SBRT for untreated solitary HCC patients.

By multivariate analysis, the maximum tumor diameter > 30 mm vs. ≤ 30 mm was only one prognostic factor for LCR. According to Rusthoven *et al.* [17], actuarial in-field local control rates at one & two years after SBRT of 60 Gy in 3 fractions for the treatment of 47 patients with one to three hepatic metastases (63 lesions) were 95% & 92% and 2-year local control was 100% among lesions with maximal diameter of 3 cm or less.

However, this study has some limitations in that it is a retrospective and multi-institutional series with a relatively short follow-up period. The group is very heterogeneous including primary and metastatic liver tumors. That is why the irradiated dose and the follow-up method are inconsistent, too. The reason why there was no difference by the stratification of irradiated dose may be that in this study the problem of algorithm or prescription point can be integrated. We are planning to start a multi-institutional prospective large-scale clinical trial that standardized these factors.

Conclusions

There was no difference in LCR between liver metastasis vs. HCC and the higher vs. lower BED_{10} against SBRT for liver cancer except for the bigger vs. smaller tumor diameter. SBRT is a safe treatment and may be an alternative option for patients with liver tumor unfit for resection or RFA. Further prospective studies are warranted to validate the effect of SBRT for liver tumor.

Competing interests

The authors have no conflict of interest to disclose with respect to this presentation.

Authors' contributions

HY and HO carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. YM, NM, YM, TN, and TK were gave clinical data in their own institution and corrected the manuscript. KN corrected the manuscript. All authors read and approved the final manuscript.

Author details

[1]Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. [2]Department of Radiology, University of Yamanashi, Yamanashi, Japan. [3]Department of Radiology, Niigata Cancer Center Hospital, Niigata, Japan. [4]Department of Radiation Oncology, National Cancer Center Hospital, Singapore, Singapore. [5]Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan. [6]Department of Radiation Oncology, Yamagata University Hospital, Yamagata, Japan.

Received: 20 January 2014 Accepted: 21 April 2014
Published: 10 May 2014

References

1. Arii S, Sata M, Sakamoto M, Shimada M, Kumada T, Shiina S, Yamashita T, Kokudo N, Tanaka M, Takayama T, Kudo M: **Management of hepatocellular carcinoma: Report of Consensus Meeting in the 45th Annual Meeting of the Japan Society of Hepatology (2009).** *Hepatol Res* 2010, 40:667–685.
2. Yamashita H, Nakagawa K, Shiraishi K, Tago M, Igaki H, Nakamura N, Sasano N, Siina S, Omata M, Ohtomo K: **Radiotherapy for lymph node metastases in patients with hepatocellular carcinoma: retrospective study.** *J Gastroenterol Hepatol* 2007, 22:523–527.
3. Garrean S, Hering J, Saied A, Helton WS, Espat NJ: **Radiofrequency ablation of primary and metastatic liver tumors: a critical review of the literature.** *Am J Surg* 2008, 195:508–520.
4. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK: **Analysis of radiation-induced liver disease using the Lyman NTCP model.** *Int J Radiat Oncol Biol Phys* 2002, 53:810–821.
5. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, Takayasu K, Nakanuma Y, Makuuchi M, Matsuyama Y, Monden M, Kudo M: **Report of the 18th follow-up survey of primary liver cancer in Japan.** *Hepatol Res* 2010, 40:1043–1059.
6. Rhim H, Lim HK: **Radiofrequency ablation for hepatocellular carcinoma abutting the diaphragm: the value of artificial ascites.** *Abdom Imaging* 2009, 34:371–380.
7. Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y, Kubota K, Zucchi A: **No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach.** *Arch Surg* 1999, 134:984–992.
8. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC: **Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less.** *Gut* 2005, 54:1151–1156.
9. Yamashita H, Nakagawa K, Shiraishi K, Tago M, Igaki H, Nakamura N, Sasano N, Shiina S, Omata M, Ohtomo K: **External beam radiotherapy to treat intra- and extra-hepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation.** *J Gastroenterol Hepatol* 2006, 21:1555–1560.
10. Herfarth KK, Debus J, Lohr F, Bahner ML, Rhein B, Fritz P, Höss A, Schlegel W, Wannenmacher MF: **Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial.** *J Clin Oncol* 2001, 19(1):164–170.
11. Wada H, Takai Y, Nemoto K, Yamada S: **Univariate analysis of factors correlated with tumor control probability of three-dimensional conformal hypofractionated high-dose radiotherapy for small pulmonary or hepatic tumors.** *Int J Radiat Oncol Biol Phys* 2004, 58(4):1114–1120.
12. Kavanagh BD, Schefter TE, Cardenes HR, Stieber VW, Raben D, Timmerman RD, McCarter MD, Burri S, Nedzi LA, Sawyer TE, Gaspar LE: **Interim analysis of a prospective phase I/II trial of SBRT for liver metastases.** *Acta Oncol* 2006, 45(7):848–855.
13. Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, Kiil Berthelsen A, Grau C, Aage Engelholm S, Von der Maase H: **Phase II study on stereotactic body radiotherapy of colorectal metastases.** *Acta Oncol* 2006, 45(7):823–830.
14. Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, Okunieff P: **Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases.** *Int J Radiat Oncol Biol Phys* 2007, 67(3):793–798.
15. Goodman KA, Wiegner EA, Maturen KE, Zhang Z, Mo Q, Yang G, Gibbs IC, Fisher GA, Koong AC: **Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies.** *Int J Radiat Oncol Biol Phys* 2010, 78(2):486–493.
16. Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, Cummings B, Ringash J, Tse RV, Knox JJ, Dawson LA: **Phase I study of individualized stereotactic body radiotherapy of liver metastases.** *J Clin Oncol* 2009, 27:1585–1591.
17. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, Chidel MA, Pugh TJ, Franklin W, Kane M, Gaspar LE, Schefter TE: **Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases.** *J Clin Oncol* 2009, 27:1572–1578.
18. Rule W, Timmerman R, Tong L, Abdulrahman R, Meyer J, Boike T, Schwarz RE, Weatherall P, Chinsoo Cho L: **Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases.** *Ann Surg Oncol* 2011, 18:1081–1087.
19. Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, Dinniwell R, Brierley J, Kavanagh BD, Dawson LA, Schefter TE: **Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis.** *Cancer* 2011, 117:4060–4069.
20. Fumagalli I, Bibault JE, Dewas S, Kramar A, Mirabel X, Prevost B, Lacornerie T, Jerraya H, Lartigau E: **A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases.** *Radiat Oncol* 2012, 7:164.

21. Takeda A, Kunieda E, Ohashi T, Aoki Y, Koike N, Takeda T: **Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer.** *Radiother Oncol* 2011, **101**(2):255–259.
22. Murakami T, Imai Y, Okada M, Hyodo T, Lee WJ, Kim MJ, Kim T, Choi BI: **Ultrasonography, computed tomography and magnetic resonance imaging of hepatocellular carcinoma: toward improved treatment decisions.** *Oncology* 2011, **81**(Suppl 1):86–99.
23. Bruix J, Sherman M: **Management of hepatocellular carcinoma: an update.** *Hepatology* 2011, **53**:1020–1022.
24. European association for the study of the liver; European organisation for research and treatment of cancer: **EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma.** *J Hepatol* 2012, **56**:908–943.
25. Lencioni R, Llovet JM: **Modified RECIST (mRECIST) assessment for hepatocellular carcinoma.** *Semin Liver Dis* 2010, **30**:52–60.
26. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M, Dawson LA: **Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma.** *J Clin Oncol* 2008, **26**:657–664.
27. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R: **Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications.** *Radiother Oncol* 2010, **94**:1–11.
28. Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J, Johnstone PA, Cardenes HR: **Stereotactic body radiotherapy for primary hepatocellular carcinoma.** *Int J Radiat Oncol Biol Phys* 2011, **81**:e447–e453.
29. Kang JK, Kim MS, Cho CK, Yang KM, Yoo HJ, Kim JH, Bae SH, Jung da H, Kim KB, Lee DH, Han CJ, Kim J, Park SC, Kim YH: **Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization.** *Cancer* 2012, **118**:5424–5431.
30. Blomgren H, Lax I, Näslund I, Svanström 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.
31. Cardenes HR, Price TR, Perkins SM, Maluccio M, Kwo P, Breen TE, Henderson MA, Schefter TE, Tudor K, Deluca J, Johnstone PA: **Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma.** *Clin Transl Oncol* 2010, **12**:218–225.
32. Kwon JH, Bae SH, Kim JY, Choi BO, Jang HS, Jang JW, Choi JY, Yoon SK, Chung KW: **Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer.** *BMC Cancer* 2010, **10**:475.
33. Louis C, Dewas S, Mirabel X, Lacornerie T, Adenis A, Bonodeau F, Lartigau E: **Stereotactic radiotherapy of hepatocellular carcinoma: preliminary results.** *Technol Cancer Res Treat* 2010, **9**:479–487.
34. Seo YS, Kim MS, Yoo SY, Cho CK, Choi CW, Kim JH, Han CJ, Park SC, Lee BH, Kim YH, Lee DH: **Preliminary result of stereotactic body radiotherapy as a local salvage treatment for inoperable hepatocellular carcinoma.** *J Surg Oncol* 2010, **102**:209–214.
35. Goyal K, Einstein D, Yao M, Kunos C, Barton F, Singh D, Siegel C, Stulberg J, Sanabria J: **Cyberknife stereotactic body radiation therapy for nonresectable tumors of the liver: preliminary results.** *HPB Surg* 2010, **2010**. doi: 10.1155/2010/309780.
36. Son SH, Choi BO, Ryu MR, Kang YN, Jang JS, Bae SH, Yoon SK, Choi IB, Kang KM, Jang HS: **Stereotactic body radiotherapy for patients with unresectable primary hepatocellular carcinoma: dose-volumetric parameters predicting the hepatic complication.** *Int J Radiat Oncol Biol Phys* 2010, **78**:1073–1080.
37. Dawood O, Mahadevan A, Goodman KA: **Stereotactic body radiation therapy for liver metastases.** *Eur J Cancer* 2009, **45**:2947–2959.
38. van Laarhoven HW, Kaanders JH, Lok J, Peeters WJ, Rijken PF, Wiering B, Ruers TJ, Punt CJ, Heerschap A, van der Kogel AJ: **Hypoxia in relation to vasculature and proliferation in liver metastases in patients with colorectal cancer.** *Int J Radiat Oncol Biol Phys* 2006, **64**:473–482.
39. McCammon R, Schefter TE, Gaspar LE, Zaemisch R, Gravdahl D, Kavanagh B: **Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy.** *Int J Radiat Oncol Biol Phys* 2009, **73**:112–118.
40. Takeda A, Sanuki N, Eriguchi T, Kobayashi T, Iwabutchi S, Matsunaga K, Mizuno T, Yashiro K, Nisimura S, Kunieda E: **Stereotactic ablative body radiotherapy for previously untreated solitary hepatocellular carcinoma.** *J Gastroenterol Hepatol* 2013, **29**:372–379.

doi:10.1186/1748-717X-9-112
Cite this article as: Yamashita *et al.*: Local effect of stereotactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients. *Radiation Oncology* 2014 **9**:112.

創刊60周年記念特集
癌治療この10年(2004～2014年)，そして未来への展望
放射線領域

リニアック治療の現状と将来—浮き彫りになった課題

大西　洋[*1]

Present Status and Prospect of Radiotherapy using Linear Accelerator -Outstanding Problems：Onishi H[*1](*1Department of Radiology, University of Yamanashi)

The technological advancement of linear accelerator (Linac) is remarkable and it has enabled beams convergence only to tumor area. Japanese radiation therapy-related structure is expected to have a long development in future owing to a super aging society and the international standardization of the cancer treatment. Though the proper number of radiation oncologists is relatively small compared to the number of linac machines, the latter has been increasing now.There must be sufficient number of experienced staffs for operation of high precision radiotherapy and its safe and efficient management needs a centralization rather increase of institutions. A proper cost-effectiveness analysis and well-balanced arrangement for the ratio of staff to equipment have been more important

Key words：Linear accelerator, Present data, Future problem, Japanese structure, Centralization

Jpn J Cancer Clin **60** (6)：627～635，2014

はじめに：放射線治療を取り巻く10年間の環境変化

日本では概ね2人に1人ががんに罹り，3人に1人ががんで亡くなる時代である．すなわち，がんは最も身近でありふれた最期のありかたであるといえる．現在日本ではがんに罹った患者のうち約3割弱程度が放射線治療を受けているが，この割合は他の多くの国では5割以上であり，Evidenceに基づいた国際的ながん治療の標準化により，放射線治療施行割合は国際的な平均値に近づきつつある[1]．さらに日本では近い将来，世界でも類を見ない超高齢化社会（5人に1人が75歳以上）が予測され，必然的に低侵襲な治療のニーズがより高まる．ここに患者個人の意志に基づくQOL重視の傾向も加わって，近い将来日本人の4人に1人以上が生涯で一度は放射線治療を受けるような時代になると推測されている．したがって，放射線治療はこれから少なくとも半世紀は需要が増大し，関連産業は成長過程に乗り続けるであろう．そこで最も重要なのは，装置・施設・スタッフの適正な配置であり，限られたスタッフでバランス良く安全に放射線治療を提供するかが大きな課題である．

政府は2007年にがん対策基本法を施行し，これに基づき厚生労働省はがん対策推基本計画に放射線治療の充実のための補正予算を盛り込んで，がん診療連携拠点病院への放射線治療装置の配備を推進して均てん化を促した．しかし，放射線治療専門医が少ないことと装置の高額化により厚労省の描いたような均てん化は進まなかった．新しいがん対策推進基本計画（平成24年6月）においては，「国や地方公共団体は，拠点病院をはじめとする入院医療機関などと，放射線療法の質を確保し，地域格差を是正し均てん化を図るととも

*1 山梨大学医学部放射線医学講座

に，人員不足を解消する取組に加えて，一部の疾患や強度変調放射線治療などの治療技術の地域での集約化を図る」，「放射線治療機器については，先進的な放射線治療装置，重粒子線や陽子線治療機器などの研究開発を推進するとともに，その進捗状況を加味し，医療従事者等が協力して，国内での計画的かつ適正な配置を検討すること」とし，いたずらに均てん化だけを求めるのではなく，集約化という方向付けを示している[2]．具体的には，がん診療連携拠点病院の施設要件がより高レベルなもの（放射線治療医師の専従化・医学物理士や有資格専従看護師の配備の言及など）に改定される一方で，これと連携する「地域がん診療病院」では放射線治療医師も照射装置も施設要件とはなっていない．拠点病院と地域がん診療病院の間の距離・交通手段・拠点病院の病床数などの問題で，「放射線治療の連携」は事実上不可能，という声も多く聞かれる．また新制度においては，地域がん診療病院おいて照射装置の有無が規定されていないため放射線治療機器業界にとっては逆風になる可能性もある一方で，拠点病院での新規装置への更新や新規導入に拍車がかかることも考えられる．新制度の運用が進んだ時点で，放射線治療装置の配備状況を分析して適切な連携が達成されているかどうか十分な検証が必要であろう．

また一方で，がん対策基本法は大学改革として「がんプロフェッショナル養成プラン」の設立を後押ししたが，大学院のインテンシブコースとして多数養成された「医学物理士」は放射線治療現場における職制が定まらないままで野放しにされているという大きな問題点も残されている．

1 ◆ 放射線治療関連装置の10年間の変化

20世紀には病院のお荷物的存在であった放射線治療は，より安全で確実にがん治療に貢献できるようになり，根治的にも緩和的にも放射線治療のがん治療における意義と役割は急速に見直されている．ここに最先端技術の医療応用という新規性と黒字医療分野としての経済性が加わって，経営サイドの購入意欲も高い．図1に全国の年度別のリニアック数変遷を示す．また図2にリニアックの年次別更新装置数を装置の導入後年数別に示す．これらから，リニアック装置総数は毎年約20台増加しており，さらに比較的新しい装置をより高精度な装置に更新する動きが近年目立ってきているようにみえる．図3にリニアックの年間販売台数の内容別年度別推移を示す．2007年以降の3年間の販売台数増加は，がん対策基本法の施行による補正予算の配分により旧型リニアックの更新が積極的に進められた動きを示していると考えられる．図4に日本放射線腫瘍学会（JASTRO）の構造調査[3]による年度別の高精度放射線治療装置可能な施設数の推移を示す．近年，体幹部定位放射線治療（SABR）や強度変調放射線治療（IMRT）の可能な機能を搭載した装置が急速に導入されたものと推測される．

リニアック照射装置関連の最近の10年間の技術進歩は以下のようなものが挙げられる．

①画像誘導：従来のリニアックグラフィによる照合から，透視画像またはon-rail CT，on-board kilovolt cone-beam CT（KVCBCT），megavolt cone-beam CT（MVCBCT），megavolt fan-beam CT（MVFBCT）によるmm以下の単位での照合が可能になった．

②強度変調：step and shoot法，dynamic collimator法，binary collimator法，などが基本にあり，線量率や回転速度を調整できるVMAT法が新しい手法として応用されている．

③呼吸性移動対策：従来の呼吸抑制法から，停止・同期・追尾といった新技術と呼吸換気量インジケータ使用の普及が進んだ．

④加速管の小型化：トモセラピー・サイバーナイフ・Veroなどに新規装置応用され，高速回転・ロボットアーム把持・振り子運動などを用いた照射が可能になった．

⑤線量率の増加：フラットニングフィルタフリーにすることにより線量率の大幅な増加が可能になり，従来長時間かかっていた定位照射や強度変調照射の照射時間の短縮が可能になった．

⑥治療計画装置の進歩：計算速度の飛躍的向上・アルゴリズムの精密化・自動輪郭抽出などの技術進歩が急速に進んだ．

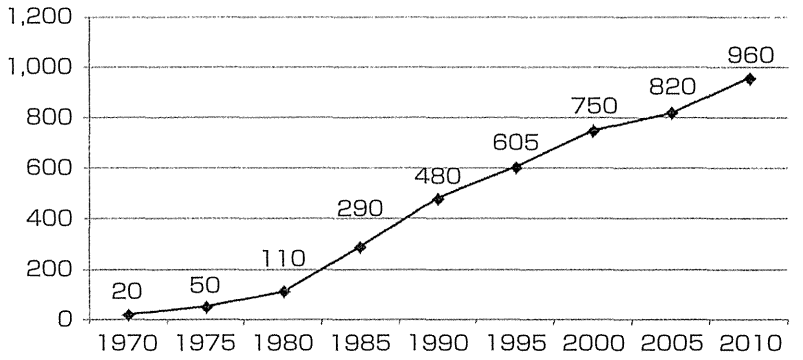

図1　全国の年度別のリニアック数推移

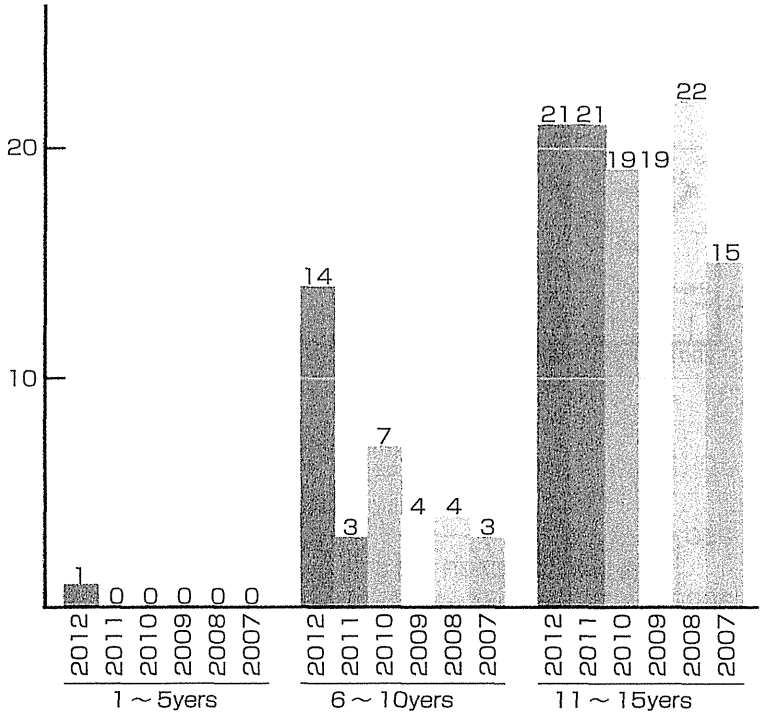

図2　リニアックの導入後年数別・年度別更新装置数更新装置数

図5～8に代表的な先進リニアック装置を示す．以上のような技術革新が常に進行しているが，常に最先端の技術と開発費用が必要とされることから，リニアックメーカサイドとしても淘汰が進んだ．この10年で三菱電機とシーメンス社がリニアック製造販売から撤退を表明した一方で，トモセラピー社，アキュレイ社，三菱重工業社が新規参入を果たした．また，平成26年度からは遠隔コバルトの診療報酬が廃止された．

2 ◆ 放射線治療の医療費

現在のいわゆる高精度照射技術の保険導入年度は，表1に示すようにほぼ最近の10年間に集中している．また，2004年以降の放射線治療の主な項目について，平成14年（または保険収載時）を1とした相対的な点数の推移を図9に示す．平成20年以降放射線治療の診療報酬は相当な評価

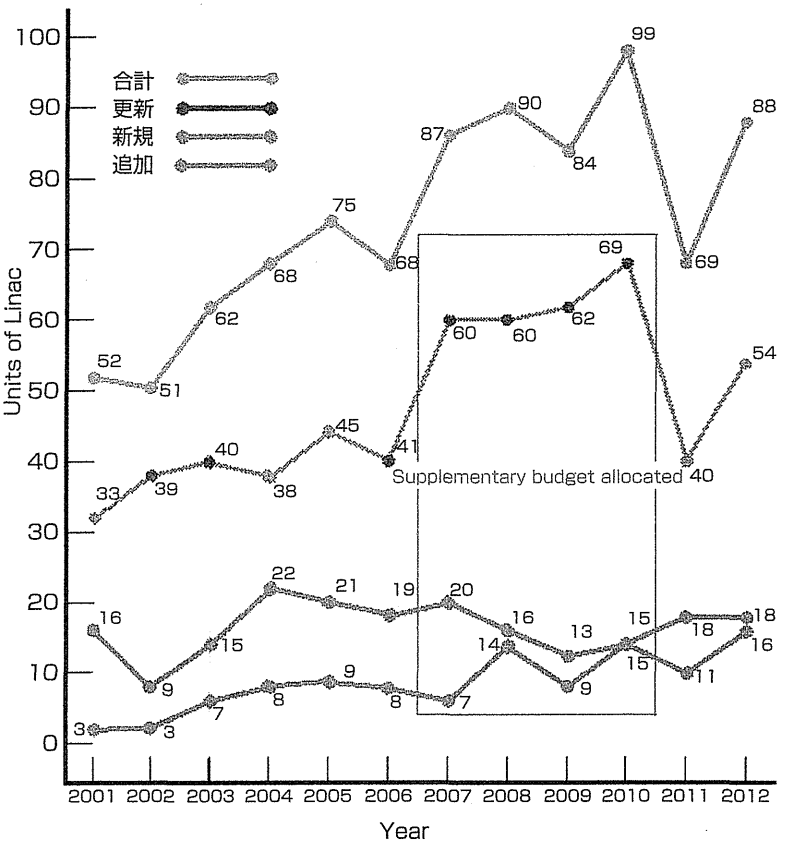

図 3　リニアックの年間販売台数の年度別推移

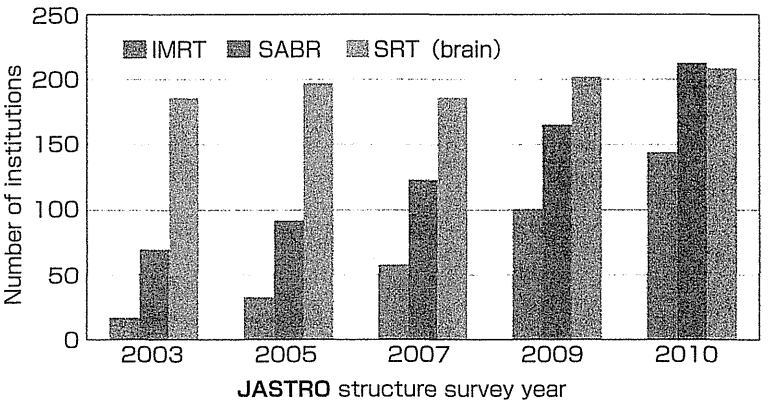

図 4　厚労省がん研究助成金計画研究班手島班 (14-6)：がんの集学的治療における放射線腫瘍学—医療実態調査研究に基づく放射線治療の品質確保に必要とされる基準構造

を受け増加していることが分かる．がん医療費に占める放射線治療の比率の変化を図 **10** に示す．がん治療医療費全体の年平均増加率は 2005 年から 2010 年間の 4.3％で，化学療法は 1.1％に対して，手術は 9.0％，放射線治療は 9.8％と高率であったとはいえ，がん医療費に占める放射線治療の比率

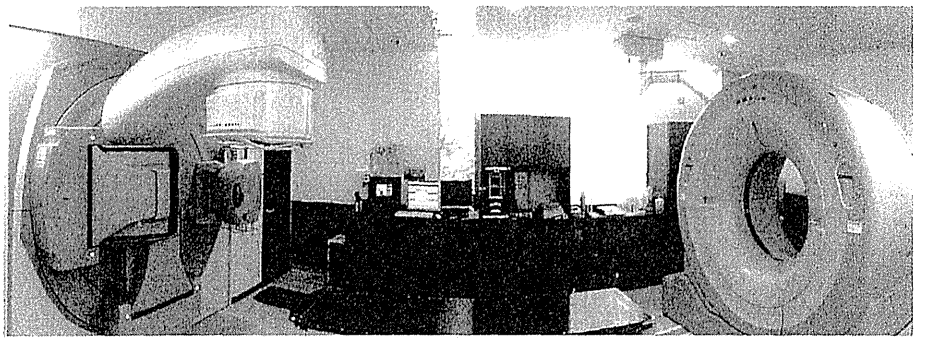

図5 CT on rail system
診断用16列large bore CTがKVCBCT撮影可能なリニアックと一体化している.

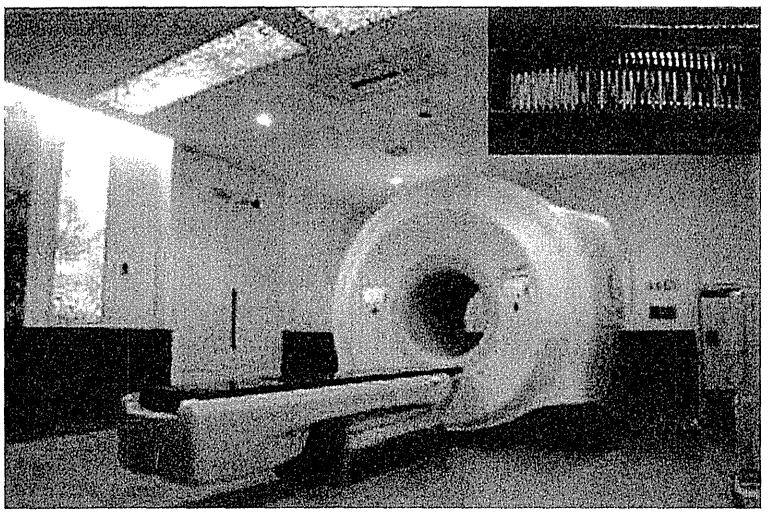

図6 Tomotherapy
MVFBCT機能搭載し，小型化加速管の高速回転ヘリカル照射とバイナリコリメータ使用による高精度IGRT/IMRT専用装置.

は手術や化学療法に比べると少ないように思われる.

3 放射線治療患者数と必要リニアック数の将来予測

放射線治療患者数は着実に増加しておりこの10年で2倍に増加して現在年間約20万人が放射線治療を受けているが，年間のがん罹患患者数が約80万人である[4]こと，その半分以上は放射線治療の適応があると想定されること，複数回の放射線治療を受ける患者が1割以上いると考えられること，さらに表2のような理由によって，放射線治療の患者数は10年後には年間少なくとも40万人以上になると推測される．一方で，厚労省がん研究助成金計画研究手島班の「がんの集学的治療における放射線腫瘍学—医療実態調査研究に基づく放射線治療の品質確保に必要とされる基準構造－通称Japanese Blue Book」[5]に基づき，1台のリニアックあたりの年間照射患者適正数を300人と想定すると1,300台の装置が必要になり，今後さらに500台程度の増加が必要とされる．ただし，放射線治療ががんに対する外科内科を含めた集学的治療の一部であること・放射線治療専門医数・収益効率などから考えて他科診療と合体した，照射装置配置のセンター化が急務であろう.

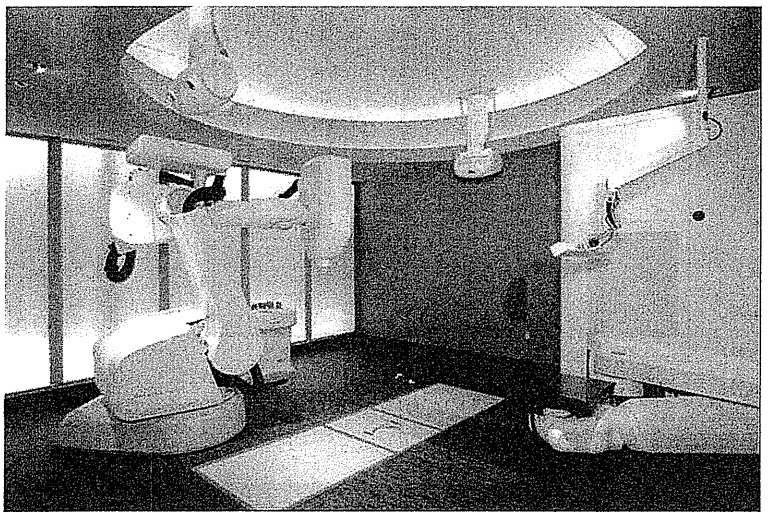

図7 サイバーナイフ
2方向からの透視下に画像誘導を行い，肺がんに対してはマーカレスの追尾照射が可能．ロボットアームを用いたアイソセンタを持たない最大1,200門のビームにより高い線量集中性を実現．

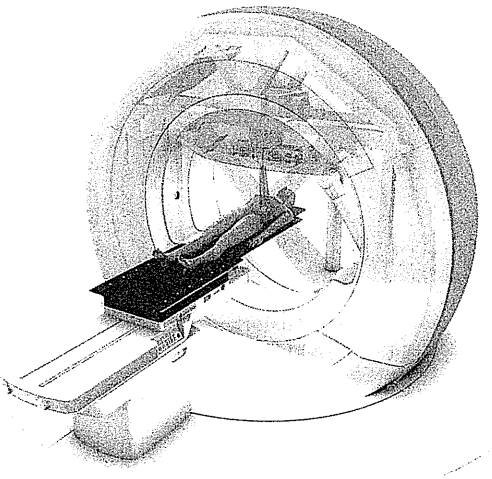

図8 Vero-4DRT
照射ガントリー内に2方向透視装置を搭載しKVCBCT撮影可能。振り子機能を持った小型化加速管により追尾照射が可能。

4 ❁ 日本の放射線治療の将来戦略

冒頭に述べたが，日本の社会構造上放射線治療関連産業は今後も成長がほぼ確実で，がん診療における意義と役割を考えると，医療費的にも増額することが許容されるのではないかと考える．しかし，医療費の支払いの多くが税金で成り立っている以上不健全な成長はゆるされない．新医療技術の発展のインセンティブも普及（販売）も診療報酬次第であるが，日本の診療報酬は学会という専門家集団からの提案（要望）に沿って検討され，その決定のプロセスには患者の声も大きく反映される．患者に対する診療内容を国が一律には規定

表1　リニアック関連の先端放射線治療技術と医療保険導入年

照射技術	医療保険導入年
直線加速器により定位放射線治療	2004
強度変調放射線治療	2008
医療機器管理料2	2008
画像誘導放射線治療	2010
呼吸制移動対策	2012

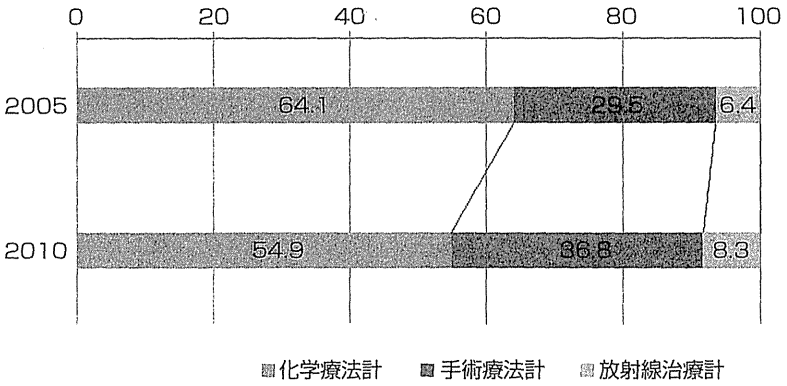

図9　がん医療費に占める化学療法，手術，放射線治療の比率の変化（「国民医療費の概況」報告書と「社会医療診療行為」の調査データより推計）

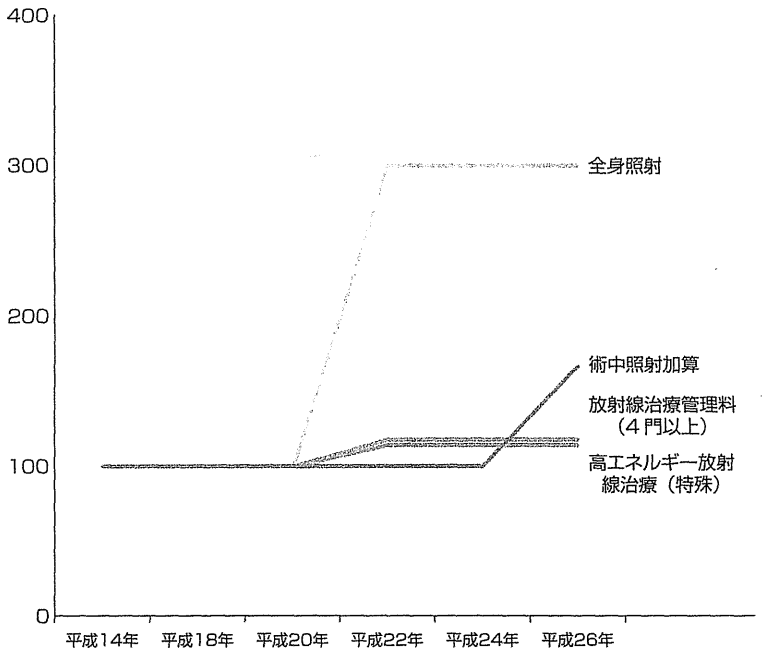

図10　放射線治療のリニアック関係の主な診療報酬の10年間の変遷
平成14年（または保険収載時）を1とした相対的な点数の推移.

表2　将来の放射線治療需要を増やす因子

高齢化社会に伴うがん患者の増加と低侵襲治療の必要性
Evidence Based Medicine の更なる普及とがん治療法のグローバル化
治療法の自己選択の普及と意識向上
QOL 重視の治療方針
医療費削減
医療政策（がん対策基本法）による放射線治療の重要視
照射技術の更なる進歩

していないが，今回の診療報酬で乳がんの寡分割照射の算定必要要件に「JASTRO が作成した最新の放射線治療計画ガイドラインを遵守して実施した場合に限り算定できる」と明記されたことは，JASTRO が正当な評価と信頼を受けているものと判断されると同時に JASTRO が負っている責任の重大さを示している．安全で効率的な高精度放射線治療を達成するには，スタッフと装置の集約化は避けて通れないであろう．

日本の将来のがん診療において放射線治療の意義の大きさを考えたとき，JASTRO の果たすべき役割と責任は極めて大きい．また新技術の導入の際には国民が個人レベルの期待や要望のみに基づいた声を上げるのはなく，「常に公共の福祉のために利用されるべき基本的人権」という憲法12条の理念を尊重しなくてはならない．将来の放射線治療機器の適切な配置は JASTRO の判断と国民の声が握っていることを強調しておきたい．また，放射線治療関連の企業サイドには，放射線津料の質と安全が保たれるように，当該施設の実態（スタッフ数と質）について事前調査と評価を行い，適切な販売活動の展開を期待する．「売れれば良い」といった無責任な販売行為は，一過性には利益をもたらすかもしれないが，長い目でみると，将来の放射線治療の信頼低下を招き結果的に損失につながりかねない[6]ことを知っておく必要がある．放射線治療ががん診療と国民生活の基盤的文化ともなるべく，医療側・企業側・政府側ともに慎重で堅実な戦略的態度[7]が重要となるであろう．

おわりに

近年の放射線治療は，高精度照射技術の進歩とともに2006年策定のがん対策基本法など政策的な配慮もあり，診療的にも病院経営的にも目立った存在になって来ている．装置数と医師数のバランスからいえばやや装置数が過剰になってきている昨今であるが，依然として新規の放射線治療施設は増えていることや，先端照射装置への入れ替えも盛んであることが明らかになった．このような現状の中で放射線治療産業は活況を呈するようになってきたが，高精度治療の発展故に十分なスタッフが必要であり，照射施設数が増えることよりセンター化をめざすことの重要性がさらに増している．

一方で，米国では Obama Care の導入により医療費抑制と皆保険化をめざす中で，強度変調放射線治療や陽子線治療の診療費は低く抑えらている．日本では米国とは異なりようやく放射線治療が本来得るべき役割と評価を徐々に獲得する中で放射線治療機器業界も発展してきているが，今後も放射線治療界が健全かつ適正に発展を続けるために，限られた医療費というパイの中で適切な費用対効果分析がなされるべきである．また，最先端リニアック照射や粒子線治療などの新規技術については，ともすれば民間施設主導で展開される傾向にあるが，安全性と有効性については研究施設による科学的評価が必須であり，装置と人員のバランスの良い配置も含めて JASTRO による適切な戦略の立案と国民の理解が重要になるであろう．放射線治療における「質・量」に目を向けた

時，早急に対処すべき課題は放射線治療を支える専門職の集団の質である．質の改善に向けた努力に対しての診療報酬の項目追加，既存項目の報酬額の増額がより安全な放射線治療を支える基盤となるはずである．

謝辞

最後に，本稿の資料作成に多くのご協力とご指導をいただきました，芦野靖夫様（CMS Japan），谷義正様（ユーロメディテック），後藤正治様（バリアンジャパン），手島昭樹先生（大阪成人病センタ），沼崎穂高先生（大阪大学），土器屋卓志先生（埼玉医科大学名誉教授）らに心より御礼申し上げます．

文　献

1) 大西洋：がん放射線治療2010，篠原出版新社，東京，2010
2) http://www.mhlw.go.jp/bunya/kenkou/gan_byoin.html
3) http://www.jastro.or.jp/aboutus/datacenter.php
4) http://ganjoho.jp/public/statistics/pub/statistics01.html
5) http://iss.ndl.go.jp/books/R100000002-I000007707465-00?ar=4e1f
6) 大西　洋，荒木　力，山下　孝・他：わが国の放射線治療スタッフと治療機器配備状況－放射線治療の品質保証と医療ミス削減のために．癌と宿主 **16**：191-199，2004
7) 大西　洋，荒木　力，中川恵一：放射線治療現場の人材不足の現状と対策．映像情報 **37**：1231-1235，2005

「最新照射技術は最良か？」
―総論的考察

大西 洋
山梨大学医学部放射線科

要旨：「最新」は客観的・絶対的・物理的な評価軸だが、「最良」は主観的・相対的・概念的な評価軸であり、「最新は最良か？」という問いに対する回答は施設側・装置側のさまざまな要素によって判断が異なる。重要なのは、最新にこだわる必要は必ずしもなく、施設ごと・患者ごとに良悪に関する判断基準を正確に定め、その根拠を明らかした上で、最良なものを選ぶことである。

「女房と畳は新しい方が良い」…古(いにしえ)の封建時代のことわざであり、今日では口が裂けても言葉に出せない言い回しであるが、「新しいものは清々しい」という意味では間違ってはいないかもしれない。特に技術系社会では、「最新」という言葉は、現場スタッフ的にもマーケティング的にも常に魅力ある誘い文句である。

ただ、一方では「女房と鍋釜は古いほど良い」という対義的ことわざもあり、そこには「阿吽の呼吸・染み付いた味・愛着・相性」といった意味が込められている。〝三丁目の夕日〟というタイトルの人気映画に込められている「古き良き」ものは「Always（good）」＝「変わらない良さ」でもある。

そんな対極的な2つの視点を共有しつつ考えた時に「最新は最良か？」という問い掛けに端的に回答するならば、「TPOによって異なる」と答えざるを得ない。「最新」は客観的・絶対的・物理的な評価軸だが、「最良」は主観的・相対的・概念的な評価軸であるためである。身近なところではパソコンのOSや携帯電話の機能など、時に「最新が間違いなく以前より悪い」場合もあり得る。

筆者が普段乗り回している日社の最新F車は、1年間で5回もリコールを繰り返しているが人気車である。さらに、瞬間的には「最新が最良」と判断できたとしても、変化が早過ぎてすぐに「新たな最新」が出現する場合には、「最新が最良」と判断する意味すら失

表1　放射線治療における「良悪」を決める判断の要素（施設側）

①	スタッフの数
②	スタッフの種類
③	スタッフの質
④	治療患者数
⑤	治療患者の種類
⑥	他科の要望
⑦	施設としてのニーズ
⑧	地域としてのニーズ
⑨	国家としてのニーズ
⑩	資金量（施設と国家の両面で）

表2　放射線治療における「良悪」を決める判断の要素（装置側）

⑪	安定性
⑫	耐久性
⑬	安全性
⑭	精度
⑮	線量集中度
⑯	速度
⑰	分かりやすさ
⑱	ネットワークとの相性
⑲	メンテナンス
⑳	価格
㉑	侵襲性

われる場合もあるだろう。

　また、メーカーサイドに立てば、「最新の装置」はマーケットニーズを反映したもの、または将来へのブレークスルーを目指したチャレンジであり、競合他社製品との差別化を考慮したものにならざるを得ない。

　したがって、「最新は最良か?」という問い掛けは、相当に個別化された条件のもとで回答を出す必要があり、おそらく最も重要なのは、「良悪に関する自己の判断基準を正確に定め、その根拠を明らかにすること」であろう。

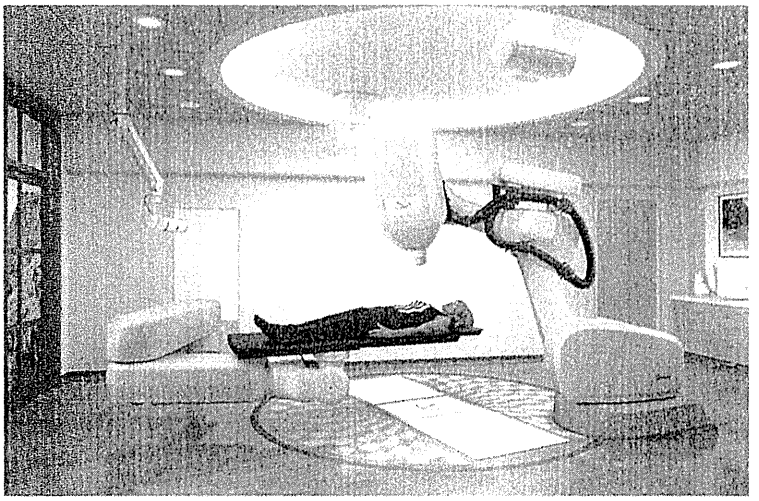

図１　技術の粋を集めた最新型サイバーナイフ装置

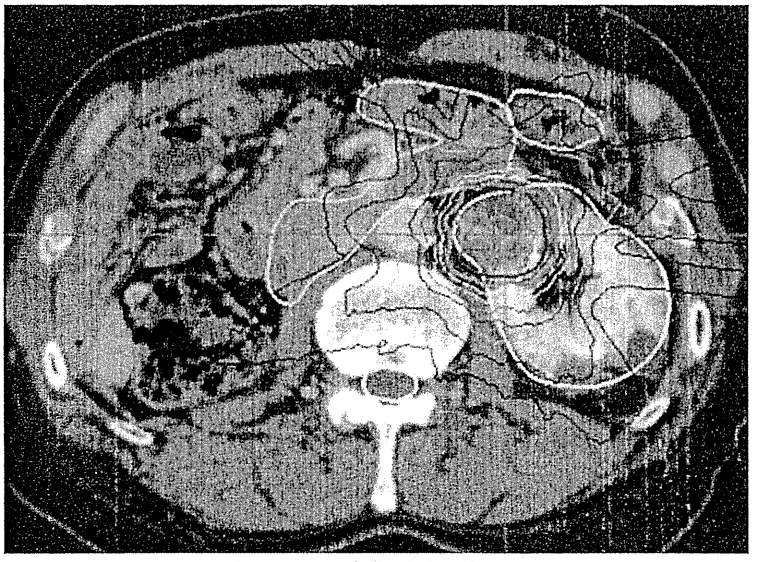

図２　サイバーナイフ装置による定位照射の線量分布
侵襲的な金マーカ埋め込みと高コストな４次元動体追尾技術が必要となる。わずかな位置ずれが効果と有害事象の両面で問題を発生する

放射線治療の良悪を決める要素

「最新」を具現するキーワードとして「イノベーション」があるが、「放射線治療」と「イノベーション」というワードで検索すると数え切れないサイトが表示される。放射線治療がいかにイノベーションと相まって発展中であるかがよく分かるが、中には相当怪しいサイトも見出される。現在のような技術革新の速度が速い社会においては、短期的ではなく中長期的な視点が重要となる。

　放射線治療における「判断を決める要素」とは、施設側と対象物品側に分けると、それぞれ表１と表２のようにまとめられると考える。施設側要素をまとめて表現すると、「施設個々の治療ニーズを他科とも相談して評価し、地域的・国家的な判断も交え、スタッフの力量と施設の資金や医療費を賄う国家の財政に見合った装置を選ぶこと」である。

　表１に挙げたさまざまな要素から、「施設ごとの最良」を判断する要素を決定するのは容易ではない。それぞれの要素について冷静かつ正確な分析を加えた上で異なる職種のスタッフで議論することと、メーカーや仲介業者との綿密な情報交換を行うことが必要である。その際には、施設側は無理なコストカットを求めないこと、販売側は利益主導に走ら

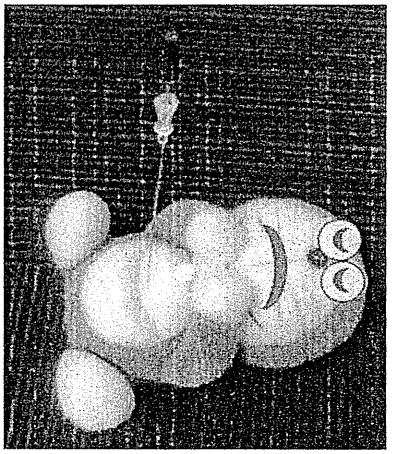

図３　経皮的金マーカ留置術（イメージ図）

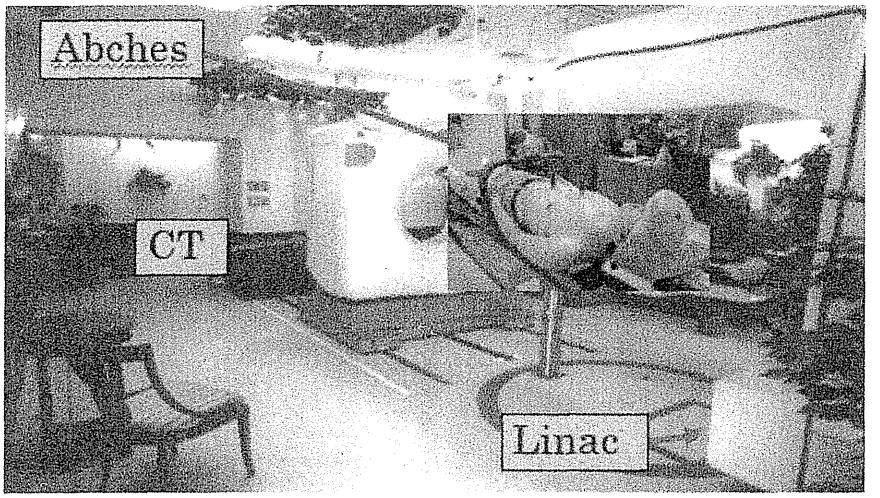

図４　従来型装置を活用したCTリニアックシステムと３次元呼吸停止法。あらゆる臓器に対してマーカレスの画像誘導と呼吸移動対策が可能である

ないことも困難だが、重要なポイントといえるであろう。

また、装置側についてはさまざまな評価指標の他、価格による対費用効果分析、さらに治療全体としての侵襲性についての評価が重要である。この場合の判断や評価は、施設ごとの治療スタッフの信念によって下される、ある意味、「好き嫌い」に基づく判断も許容されると考える。

具体例について

画像誘導技術と呼吸性移動対策を一例に挙げてみる。図1、2には、技術の粋を集めた最新型サイバーナイフ治療装置と、それによる腎癌に対する呼吸追尾技術併用の定位放射線治療の線量分布を示している。周囲の正常臓器の狭間にある腫瘍に対する最高レベルの線量集中性が実現可能だが、少しでもずれると、腸管への重篤が合併症の発生と腫瘍制御率の低下のいずれをも招く不安定性や危険性と隣り合わせである。また、高額な装置（図2）と侵襲的な金マーカの留置（図3）を必要とする。

「煩雑さ・高コスト・侵襲性」と得られる「従来法を工夫して利用した手法（CTリニアックシステムと呼吸停止法・図4）と比較してわずかに上回る（かもしれない）高精度」の意義と必要性を患者さんや腫瘍の状態ごとに比較評価して、「最新＝最良かどうか」を吟味して決めていくべきである。

まとめに代えて

我々が念頭に据えるべき視点とは

一般的には「最新装置が最良の結果に結びつく」場合が多く、一例に挙げたサイバーナイフ治療は筆者らも頻用しており、使いこなせば貴重なモダリティであることは間違いない。ただ重要なのは、「最新にこだわる必要はなく、施設ごと・患者ごとに最良なものを選ぶこと」であり、結果として、「我が古鍋釜」ともなるべき装置や手法に勤しむことである。したがって、それぞれの施設は「自分たちの患者さんにとって最良とは何か」を熟慮することが大切であり、売り手側は「最新を売りつけるのではなく、顧客と施設に応じた治療内容に沿った『最良』とは何かを引き出してあげること」が長期的な信頼を得るためにも重要な戦略であると考える。

さらに最重要なのは、「多くは国費で賄われる放射線治療費を適切に運用する」という視点であり、治療側も患者さん側も冷静な判断に基づいた「最良の放射線治療環境」を国家として構築していくことであり、我々は常にそのような視点を念頭に据える必要があるだろう。

※　※

大西　洋（おおにし・ひろし）●61年神奈川県生まれ。88年千葉大医学部卒。同年同大医学部放射線科研修医。89年山梨医科大（現・山梨大医学部）放射線科助手、92年成田赤十字病院放射線科、00年米国MDアンダーソンがんセンター・メモリアルスローンケタリングがんセンター留学。同年山梨大医学部放射線科講師、04年准教授、14年教授、および放射線部長。専門は放射線腫瘍学（特に肺がん、体幹部定位放射線照射・がん治療のIVR、悪性腫瘍画像診断）。著書に「詳説・体幹部定位放射線治療」「早期のがん治療の選択」「エビデンス放射線治療」「放射線腫瘍学」など。

International Journal of Radiation Biology, December 2014; 90(12): 1119–1124

ISSN 0955-3002 print / ISSN 1362-3095 online
DOI: 10.3109/09553002.2014.932030

informa
healthcare

Tumor induction in mice after local irradiation with single doses of either carbon-ion beams or gamma rays

Koichi Ando[1], Sachiko Koike[2], Yasushi Ohmachi[3], Yutaka Ando[2] & Gen Kobashi[4]

[1]*Heavy Ion Medical Center, Gunma University, Maebashi-shi,* [2]*Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba-shi,* [3]*Research Center for Radiation Emergency Medicine, National Institute of Radiological Sciences, Chiba-shi, and* [4]*Department of Planning and Management, National Institute of Radiological Sciences, Chiba-shi, Japan*

Abstract

Purpose: To determine the dose-dependent relative biological effectiveness (RBE) for tumor prevalence in mice receiving single localized doses to their right leg of either carbon ions (15, 45 or 75 keV/μm) or 137Cs gamma rays.

Methods and materials: A total of 1647 female C3H mice were irradiated to their hind legs with a localized dose of either reference gamma rays or 15, 45 or 75 keV/μm carbon-ion beams. Irradiated mice were evaluated for tumors twice a month during their three-year life span, and the dimensions of any tumors found were measured with a caliper. The tumor induction frequency was calculated by Kaplan-Meier analysis.

Results: The incidence of tumors from 50 Gy of 45 keV/μm carbon ions was marginally higher than those from 50 Gy of gamma rays. However, 60 Gy of 15 keV/μm carbon ions induced significantly fewer tumors than did gamma rays. RBE values of 0.87 ± 0.12, 1.29 ± 0.08 or 2.06 ± 0.39 for lifetime tumorigenesis were calculated for 15, 45 or 75 keV/μm carbon-ion beams, respectively. Fibrosarcoma predominated, with no Linear Energy Transfer (LET)-dependent differences in the tumor histology. Experiments measuring the late effect of leg skin shrinkage suggested that the carcinogenic damage of 15 keV/μm carbon ions would be less than that of gamma rays.

Conclusions: We conclude that patients receiving radiation doses to their normal tissues would face less risk of secondary tumor induction by carbon ions of intermediate LET values compared to equivalent doses of photons.

Keywords: High Linear Energy Transfer (LET), radiation-induced tumors, relative biological effectiveness (RBE)

Introduction

Carbon-ion radiotherapy started in 1994 in Chiba, Japan, and since then more than 9,000 patients have been treated worldwide (Particle Therapy Co-operative Group 2012). In spite of its prominent effectiveness in local tumor control, doubts remain regarding the potential risk that high-LET irradiation may induce more secondary malignancies than low-LET irradiation at low doses (Turner and Fry 1994, Scott 1997). Assessing the risk of second malignancies after radiotherapy with protons and heavy ions is also becoming a concern (Suit et al. 2007, Newhauser and Durante 2011). The concern over carbon-ion radiotherapy arises from short follow-up periods relative to the time required for the full development of late normal tissue injury, including second malignancies (Suit et al. 2010). In the case of therapeutic beams of carbon ions, Bragg peaks are spread out, which provide a range of various LET values along the beam path in which normal tissues receive intermediate LET at the entrance plateau, while deep-seated tumors are irradiated with a high-LET Bragg peak. The biological effectiveness of radiation depends on the LET, which would also apply to the carcinogenesis endpoint. We previously reported an RBE (relative biological effectiveness) value of 2.2 based on a retrospective analysis for tumor induction after single and fractionated carbon-ion irradiation (Ando et al. 2005). Since the analysis is made on data not clearly discriminating LET, because of the limited number of samples, it is necessary to clarify the LET-dependent carcinogenic risk of carbon ions. We here report on results from newly conducted experiments for carbon-ion beams, and unexpectedly explain that the carcinogenic risk of intermediate LET of carbon ions was lower than that of gamma rays.

Materials and methods

Mice and irradiation

C3H/HeMsNrsf female mice aged 12–18 weeks old were used for this study. The mice were produced and maintained in specific pathogen-free (SPF) facilities at the National Institute of Radiological Sciences. Two types of the experiments were included here: One was to observe tumor induction after radiation, and the other was to investigate late skin shrinkage. A total of 1797 mice were used in these experiments: 1647 mice for the tumor induction and 150 mice for

Correspondence: Prof. Koichi Ando, D.D.S., Ph.D., D.M.Sc. Heavy Ion Medical Center, Gunma University, Showa-machi 3-39-22, Maebashi-shi, Gunma, Japan 371-8511. Tel: + 81 27 220 8378. Fax: + 81 27 220 8114. E-mail; kando3@air.email.ne.jp

(Received 6 January 2014; revised 18 February 2014; accepted 24 May 2014)

the skin shrinkage. Five mice were used for all treated and control groups. No data previously reported (Ando et al. 2005) are included here.

Carbon-12 ions were accelerated by the HIMAC synchrotron up to 290 MeV/u (Kanai et al. 1999). Exposures were conducted using horizontal carbon beams with a dose rate of approximately 3 Gy/min. The LET of 290 MeV/u carbon ions was 14 keV/μm at the entrance of a 6-cm SOBP (Spread-Out-Bragg-Peak). The depth position along the irradiation path was adjusted by a Lucite range shifter so that the LET of interest at the surface skin could be selected to use. The irradiation field was defined by using two collimators in series, one made of iron and the other of brass. The reference beam consisted of ^{137}Cs gamma rays with a dose rate of 1.6 Gy/min at an FSD of 21 cm. With pentobarbital anesthesia (50 mg/kg) and taping, five mice were immobilized on a Lucite plate to place right hind legs in a rectangular field having dimensions of 28 × 100 mm, and received single radiation doses. A doughnut-shaped radiation field with a 30-mm rim was prepared by 5-CM thick lead, and was used to collimate the vertical beam of gamma rays. The length of legs irradiated with carbon ions was therefore 2 mm shorter than that with gamma rays (30 mm minus 28 mm). The foot was excluded from the irradiation fields of any radiation qualities. Mice were immobilized on a 5-mm thick Lucite plate, and the right hind legs were placed in a 30-mm radiation field. Electron equilibrium was reached as the gamma rays pass through Lucite plate before reaching the legs of the mice. The dose ranges used were as follows: 10–80 Gy for gamma rays, 5–70 Gy for 15 keV/μm carbon ions, and 5–60 Gy for 45 and 75 keVμm carbon ions.

Data acquisition and analysis

The irradiated legs of mice were screened twice a month during their three-year life span, and the dimensions of any tumors found were measured with a caliper. One screener, S.K., measured all tumors that appeared in irradiated legs. Of all animals that developed a leg tumor, each had only one tumor. When a mass appeared in an irradiated leg that grew to reach 10 mm or larger in diameter, the mouse was euthanized and the mass was surgically removed for histological examination. Only tumors that appeared inside, or on the edge of the irradiation field, were scored. Eight mice died before sampling and one mouse of which a record was missing were excluded from the analysis. Eighteen tumors that appeared outside of irradiated legs were excluded from the analysis, but tumors growing at the edge of the irradiated area were included. Six tumors diagnosed with mammary carcinoma were excluded from analysis, since the legs did not contain mammary glands. The log-rank test with the Bonferroni correction was used to statistically analyze any difference of tumor induction between gamma rays and carbon ions.

Skin shrinkage

Cell kill damage in normal tissue caused by radiation was quantified by measuring skin shrinkage after radiation. Hairs on the mouse right hind leg were removed by applying a depilatory agent, and two tattoo spots separated by approximately 18 mm distance were made into the outer leg skin by using a commercially available tattoo machine and Indian ink 3–7 days before irradiation. Calipers were used to measure the distance between the two tattoo spots once a month until the end of the study. The ratio of the pre-irradiation distance to post-irradiation was calculated for individual mice, and the mean and standard deviations were obtained from thus-obtained ratios (Masuda et al. 1980).

Results

Time of tumor appearance

Each radiation group consisted of a similar number of mice; i.e., 442, 410, 374 or 421 for gamma rays, 15, 45 or 75 keV/μm carbon ions, respectively. The number of tumors induced by gamma rays, 15, 45 or 75 keV/μm carbon ions was 152, 78, 89 or 122, respectively (Table I). Of the total 441 induced tumors, the earliest tumor appearing after gamma-ray irradiation was observed at Day 175, while the latest tumor was detected at Day 956 (Figure 1a). For carbon-ion irradiation, the earliest tumor that appeared was at Day 243 (75 keV/μm), while the latest one was at Day 848 (45 keV/μm). The cumulative frequency of induced tumors increased with the observation period of time for any radiation qualities. We did not find any difference between carbon ions and gamma rays in the latency of tumor induction after irradiation. However, the dependency on the radiation quality was observed for the rate of tumor induction, so that tumors induced by gamma rays increased more rapidly than those by carbon ions. Whether the size of the radiation dose would affect the incidence was studied by grouping data by the dose (Figure 1b). The rate of tumor induction clearly depended on the dose for all radiation qualities. This was most prominently shown for gamma rays, so that 10 Gy induced the initial tumor at Day 628, 30 Gy at 428 and 60 Gy at Day 175. Also noted was that the rate of tumor induction increased with an increase of the

Table I. Number (%) and types of tumors induced by irradiation with gamma rays and carbon ions.

	Osteo sarcoma	Fibro sarcoma	MFH	Hemangio sarcoma	Undifferentiated sarcoma	Squamous cell carcinoma	Others	benign tumor	Total number of tumors
Gamma rays	9 (6)	127 (84)	10 (7)	1 (1)	1 (1)	3 (2)	2 (1)*a	0 (0)	152
Carbon ions 15 keV/μm	9 (12)	61 (78)	5 (6)	0 (0)	0 (0)	2 (3)	1 (1)*b	0 (0)	78
Carbon ions 45 keV/μm	9 (11)	68 (76)	6 (8)	1 (1)	0 (0)	1 (1)	3 (3)*c	1 (1)*e	89
Carbon ions 75 keV/μm	12 (10)	97 (80)	8 (7)	0 (0)	0 (0)	3 (2)	2 (2)*d	0 (0)	122

MFH, malignant fibrous histiocytoma; *a,chondrosarcoma, mixed tumor; *b,malignant shwannoma; *c, 2 myxosarcomas, hemangiopericytoma; *d, myxosarcomas; *e,osteoma, mixed tumor.

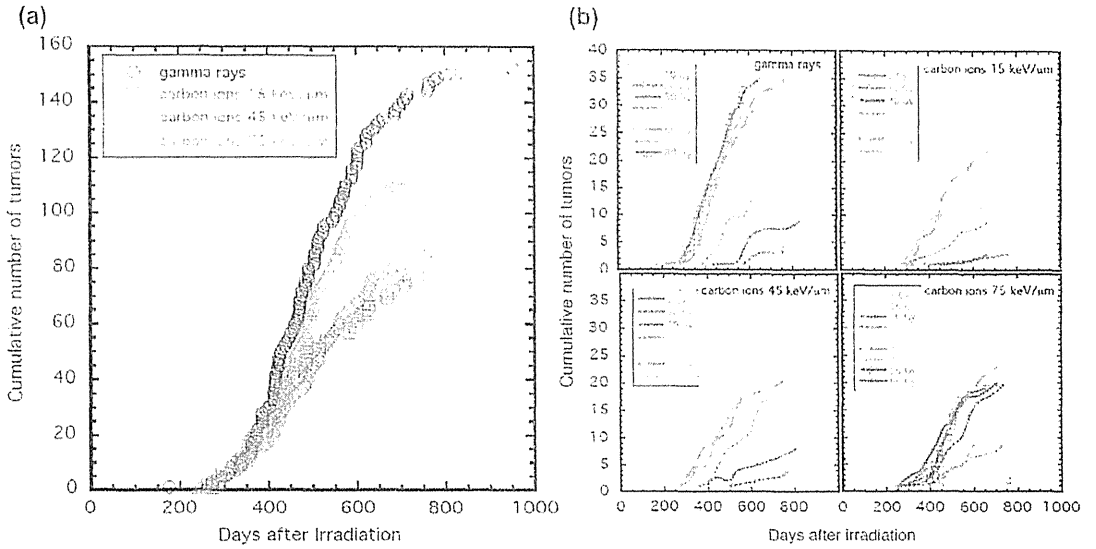

Figure 1. Cumulative number of tumors in locally irradiated mice legs. (a) Each symbol corresponds to tumors induced by single doses of gamma rays (○), carbon ions of 15 ( ), 45 (◇), or 75 keV/μm (△), respectively. All doses used in each radiation quality are included. (b) Cumulative number of induced tumors after different radiation doses. Mice received gamma rays (upper left), 15 keV/μm carbon ions (upper right), 45 keV/μm carbon ions (lower left), or 75 keV/μm carbon ions (lower right), respectively. This Figure is reproduced in color in the online version of *International Journal of Radiation Biology*.

dose up to 60 Gy, beyond which the increase of the tumor induction was less prominent or plateaued. This means that the rate of tumor appearance has a dose-limitation. A similar limitation was also observed for 45 and 75 keV/μm carbon ions. An exception to the limitation was for 15 keV/μm carbon ions, which showed a fall in the cumulative incidence after 50 Gy or larger doses.

Attrition of mice

The number of mice decreased after irradiation (Figure 2). The decrease, due to either induction of tumor or death without tumor development, was slow until 365 days after irradiation, and became prominent at 400 days or later when a significant increase of tumor induction was observed. Mice surviving irradiation decreased to 25% by Day 700. The final death was observed for a mouse that survived 1106 days after receiving 60 Gy of 75 keV/μm carbon ions.

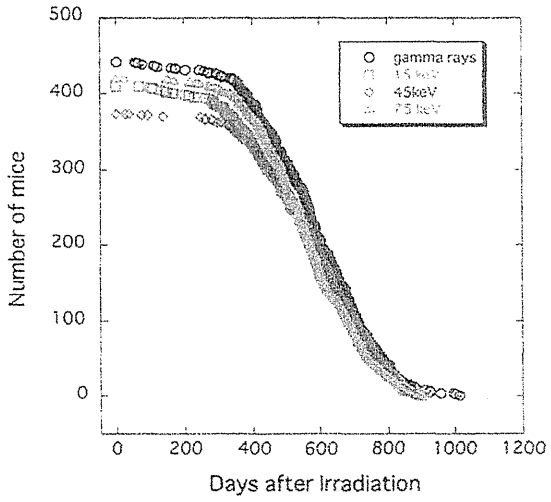

Figure 2. Number of survived mice after irradiation. Attrition of mice was due to either tumor development or death without tumor. Symbols are same as those in Figure 1(a). This Figure is reproduced in color in the online version of *International Journal of Radiation Biology*.

Dose versus tumor-incidence relation

The relation between the dose and tumor incidence was calculated for each radiation quality. We here employed the Kaplan-Meier estimator to calculate the incidence of tumor induction (Goel et al. 2010). We selected Day 700 as the time to calculate the incidence, because most tumors (75%) had developed already. For this calculation, days of death after irradiation for all mice were sorted to two categories: (1) Mice developed tumors, and therefore regarded to have died with a tumor, or (2) mice died without any tumor development. The sum of those categories gave the time of survival among mice that received irradiation. When the time of survival was multiplied by a given observation period, i.e., 700 days in our case, the incidence of tumors was calculated by the following formula: Number of mice died with tumor divided by the multiplied time of survival. It should be noted that all tumors, i.e., not only tumors that appeared before Day 700, but also those that appeared later, are included in this calculation.

Figure 3 shows the relation between the dose and the risk for carbon ions and for gamma rays. A curve fitting was made by a polynomial of cubic equation. The carcinogenic risk increased with the dose for all radiation qualities. The dose-dependent increase of risk was most prominent for 75 keV/μm carbon ions up to 35 Gy, beyond which the increase slowed down and became saturated. This

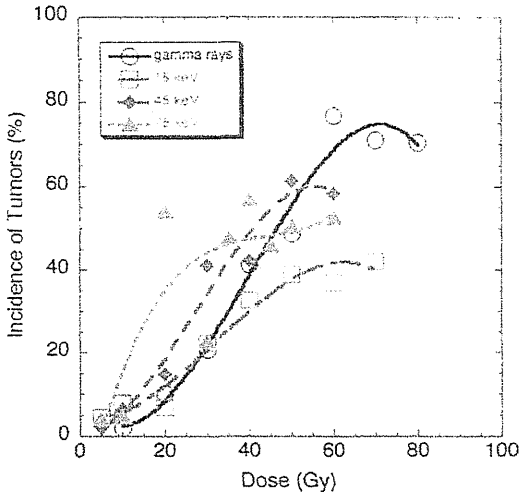

Figure 3. Dose-tumor induction relation. Tumor induction is obtained by the following equation: number of tumors / (days of tumor appeared + days of death without tumor) × 700. Symbols are same as those in Figure 1(a). This Figure is reproduced in color in the online version of *International Journal of Radiation Biology*.

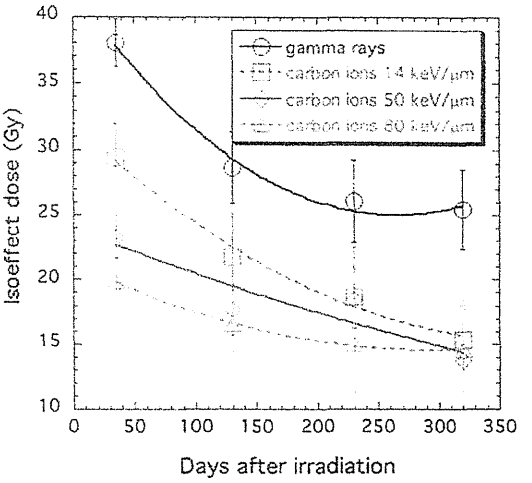

Figure 4. Isoeffect doses to cause 25% skin shrinkage in irradiated mice legs. Symbols and error bars are mean and standard deviation calculated from 20–40 mice that depends on time after irradiation. Symbols are: Gamma rays (○), 14, ( ), 50 (◇), or 80 keV/μm (△) carbon ions, respectively. LET used here are slightly but not significantly different from those used in aforementioned carcinogenic experiments. This Figure is reproduced in color in the online version of *International Journal of Radiation Biology*.

saturation was also observed for other radiation qualities, even though the level of saturation was different between radiation qualities. We compared the tumor induction between the gamma rays and carbon ions at large doses that brought about the saturation. Because a multiple comparison between all radiation qualities was used here, a p value of 0.0167 instead of 0.01 was used for the level of significance. A p value of 0.039 was obtained between gamma rays and 45 keV/μm carbon ions at 50 Gy, indicating that the incidence of tumor induction by carbon ions was slightly higher than that by gamma rays. On the other hand, tumor induction by 15 keV/μm carbon ions was significantly ($p < 0.016$) lower than that of gamma rays at 60 Gy.

We calculated the relative biological effectiveness (RBE) of carbon ions by employing isoeffect levels of 10, 15 and 20% carcinogenic risks. These values are on the ascending portion of dose-response curves. The RBE values (mean and standard deviation) thus calculated were 0.87 ± 0.12, 1.29 ± 0.08 or 2.06 ± 0.39 for 15, 45 or 75 keV/μm carbon ions, respectively.

Skin shrinkage after irradiation

We also investigated any skin shrinkage caused by the four radiation qualities. LET used in this experiment were 14, 50 and 80 keV/μm, and similar to those used for above-stated tumor induction. The isoeffect dose for 25% skin shrinkage at Day 35 was the largest for gamma rays, followed by 14, 50 and 80 keV/μm carbon ions in turn (Figure 4), and decreased when measurements were delayed. Gamma rays showed a significantly larger isoeffect dose among all radiation qualities irrespective of the time after irradiation. This means that carbon ions with any LET caused skin damage more efficiently than did gamma rays. It was noted that the difference of isoeffect dose initially observed between the three LET of carbon ions was lost at Day 320 when carcinogenesis already started in some mice.

Histology

For histological analysis, 441 tumors that appeared after irradiation were used (Table I). Of 290 carbon-ion induced tumors histologically examined, 289 tumors were malignant, while one benign tumor was osteoma. Sarcomas, such as fibrosarcoma (226 tumors; 78%), were most frequently observed followed by osteosarcoma (10%) and malignant fibrous histiocytoma (MFH) (7%). Other sarcomas observed were malignant shwannoma, myxosarcoma, hemangiopericytoma, myxosarcoma and mixed tumor. Few squamous cell carcinomas were also observed. Fibrosarcoma was also the tumor most frequently observed after gamma-ray irradiation (127 out of 152 tumors; 84%), followed by malignant fibrous histiocytoma (7%) and osteosarcoma (6%). One tumor induced by 50 Gy gamma rays was a mixed type consisting of fibrosarcoma and squamous cell carcinoma. No histological differences were noted between tumors induced by radiations of different quality.

Discussion

We found here an unexpected result that carbon ions with an intermediate LET of 14 keV/μm induced fewer numbers of tumors than gamma rays, while carbon ions with higher LET values induced greater number of tumors than did gamma rays at given doses. Radiation carcinogenesis is conceptually explained so that the incidence of radiation-induced malignancies in mice follows a bell-shape because of a balance between the incidence of transformed cells and cell killing (Chadwick and Leenhouts 1981, Hall and Giaccia 2006). This balance was experimentally shown for myeloid leukemia induction in mice after whole-body irradiation with X-rays and fission neutrons as well (Covelli et al. 1991). Watanabe reported on in vitro transformation experiments using golden

hamster embryo cells and shows a dose-dependent increase in transformants per surviving cells up to 150 R, beyond which the increase became less prominent (Watanabe et al. 1984). Tumor inductions in the present study showed a dose dependence similar to Watanabe's report and were not apparently bell-shaped, which agrees with clinical observations for patients receiving breast irradiation of up to 42 Gy for Hodgkin's disease (Hall and Giaccia 2006).

The RBE of high-LET radiation is commonly larger than unity for cell kill. This agrees with the present study, that carbon ions of any LET induced skin shrinkage more efficiently than did gamma rays at given doses (Figure 4). Because target cells for carcinogenesis in the present study could not be identified, we instead measured the leg skin shrinkage to quantify and compare the cell kill efficiencies between different radiation qualities. We previously reported that an administration of radioprotector WR-151327 prior to radiation reduced the skin shrinkage caused by gamma-ray irradiation (Matsushita et al. 1994). As protection of radiation lethality is the basic mechanisms underlying the radioprotection of phosphorothioates, including WR-151327 (Weiss 1997), any skin shrinkage would represent initial cell kill caused by irradiation in the present study. A question is why tumor induction after 15 keV/μm carbon ions was lower than that after gamma-ray irradiation. If target cells in charge of tumor development were more sensitive to carbon ions for cell kill than gamma rays, the dose-dependent increase of carcinogenesis for carbon ions would be less than that for gamma rays. This was actually the case for 15 keV/μm carbon ions in the present study (Figure 3). On the other hand, the carcinogenic risk of 45 and 75 keV/μm carbon ions was higher than that of gamma rays after 40 Gy, or below (Figure 3), even though these carbon ions killed cells more efficiently than did gamma rays (Figure 4). This suggests that the carcinogenic potential of cells surviving these high-LET radiations would be higher than that surviving gamma-ray irradiation, while the carcinogenic potential of cells surviving 15 keV/μm carbon ions would be lower than that surviving gamma-ray irradiation. In other words, the dependence of damage on LET would be different between cell kill and carcinogenesis.

The RBE values of various heavy ions for the induction of hardrian gland tumors were reported by Fry et al. (1985), and range from a value of 4 for helium-4 (228 MeV/amu) to 27 for either argon-40 (570 MeV/amu, 650 keV/μm) or iron-56 (600 MeV/amu, 190 keV/μm). Alpen et al. (1993) also reports that the RBE of helium-4 (1.6 keV/μm) for the induction of hardrian gland tumors is 2.3, and that of iron ions is 20.3 (253 keV/μm) and 39.6 (and 193 keV/μm). The dose range used to calculate these values are either below 5 Gy (Watanabe et al. 1984) or 3 Gy (Fry et al. 1985), and are much lower than that used in the present study. Recently, RBE values for acute myeloid leukemia and hepatocellular carcinoma in mice after whole body irradiation with iron-56 ions (1 GeV/amu, 150 keV/μm) have been reported by Weil et al. (2009). The initial slope of the dose-tumor incidence relation was used to calculate the RBE values of iron-56, a method also used by Fry et al. (1985) and Alpen et al. (1993). At a dose range below 1 Gy for iron ions and below 3 Gy for reference gamma rays, an RBE smaller than unity (0.475) was obtained for acute myeloid leukemia, while a large RBE of 50.9 was for hepatocellular carcinoma.

In vitro cell transformation after high-LET irradiation has also been investigated for various particles. Yang and Tobias report that an RBE of ~ 4 has been obtained for argon-40 (330 MeV/amu, 145 keV/μm) to transform C3H 10T1/2 cells while an RBE of ~ 1 is given for lower LET of carbon ions (474 MeV/amu, 10 keV/μm) at 1 Gy (Yang et al. 1985). Transformations of Syrian hamster embryo cells have been reported after irradiation with either carbon-12 or silicon-28 beams obtained by the same HIMAC accelerator as the one that we used here (Han et al. 1998). The transformation frequency in this very sensitive assay increases linearly up to 10 cGy for all LET ranging from 2.5 keV/mm (reference X-rays) and 400 keV/μm (silicon ions). The RBE values of carbon ions for transformation were found to be between 2.2 and 6.9 for LET ranging between 13 and 100 keV/μm. Using a human hybrid cell line, Bettega et al. (2009) report that the RBE values for 13.8, 29.5 or 172 keV/μm carbon ions to transform survived cells at doses below 4 Gy are 1.0, 2.5 or 12.0, respectively. They claim that the RBE values evaluated at low doses/high survival levels are larger than those at high doses/low survival levels. This claim is in line with the present in vivo study, so that RBE values of 2.17 for 75 keV/μm carbon ions are smaller than RBE values reported for others in vivo tumor induction experiments stated above (Fry et al. 1985, Alpen et al. 1993), even though the endpoints employed are totally different between ours and theirs.

The maximum frequency of tumor induction after gamma rays was higher than that after carbon ion (Figure 3). No reports referring to this kind of LET dependency could be found. In vitro transformation experiments, however, show that the maximum transformation frequency after 29.5 or 172 keV/μm carbon ions is 1.6–3-times higher than that after 15 MeV photons (Han et al. 1998). A review indicates that 15 keV/μm proton beams produced a ~ 1.5-times higher maximum transformation frequency to C3H 10T1/2 cells (Bettega 2004). A sensitive Syrian hamster embryo system also shows that the higher the LET value, the higher is the maximum transformation frequency when cells are irradiated with 2.5 keV/μm X-rays and carbon ions of up to 100 keV/μm (Han et al. 1998). These in vitro transformation experiments do not, therefore, agree with our present in vivo study. A possible explanation for the disagreement is any difference in the size of penumbra to mice between gamma rays and carbon ions. If the penumbra become larger, the number of target cells irradiated would increase. This possibility does not, however, explain why the maximum frequency after 15 keV/μm carbon ions was lower than that after higher LET of 45 or 75 keV/μm carbon ions, because an identical collimator was used for all carbon-ion irradiation.

The histological features of tumors in the present study are somehow different from those in our previous report that included data of fractionated irradiation (Ando et al. 2005). The most frequent tumors in the present study were fibrosarcoma, while those in the previous study were malignant fibrous histiocytoma, although the two studies commonly show that nearly 90% of the tumors were sarcoma. The reasons underlying the difference between the two studies are