Table 2. Subanalysis of survival

Factors	2-year OS	*P*-value by log-rank	2-year PFS	*P*-value by log-rank
Chemotherapy				
With	47.6 ± 18.7	0.10	41.4 ± 7.1	0.75
Without	53.6 ± 7.6		24.1 ± 19.5	
Tumor diameter				
Over 30 mm	55.9 ± 10.2	0.70	35.0 ± 9.2	0.34
Under 30 mm	50.3 ± 10.7		50.3 ± 9.8	
HCC type				
Hypovascular	43.2 ± 20.8	0.86	22.2 ± 13.0	0.040
Hypervascular	51.6 ± 8.4		44.2 ± 8.2	
Child–Pugh Grade				
A	53.6 ± 8.0	0.13	40.5 ± 7.5	0.22
B–C	30.3 ± 17.1		36.0 ± 16.1	
Sex				
Female	78.4 ± 11.2	0.044	67.6 ± 12.1	0.049
Male	43.1 ± 8.4		30.3 ± 7.7	
Serum AFP value				
Over 20	52.3 ± 10.9	0.81	42.1 ± 10.2	0.59
Under 20	54.8 ± 9.9		45.3 ± 9.6	
Serum PIVKA-II				
Over 35	44.7 ± 10.6	0.039	32.5 ± 9.8	0.16
Under 35	69.7 ± 9.9		54.4 ± 9.8	
BED (Gy)				
Over 100	48.1 ± 10.4	0.28	41.8 ± 10.2	0.99
Under 100	57.2 ± 9.7		39.2 ± 8.8	
Age (years old)				
Over 75	56.7 ± 10.2	0.80	54.4 ± 9.3	0.58
Under 75	49.7 ± 9.8		30.2 ± 8.6	
Hilum LN metastasis				
With	50.0 ± 35.4	0.32	0 ± 0	0.12
Without	53.5 ± 7.3		41.9 ± 6.9	
Clinical stage				
I	58.2 ± 10.8	0.40	66.3 ± 9.3	0.007
II-	50.0 ± 10.9		18.4 ± 8.0	

Continued

Table 2. Continued

Factors	2-year OS	*P*-value by log-rank	2-year PFS	*P*-value by log-rank
Primary effect				
PR/CR	56.8 ± 7.8	0.44	42.9 ± 7.5	0.24
NC/PD	38.7 ± 19.5		28.7 ± 15.3	
Performance status				
0–1	54.5 ± 7.6	0.15	37.6 ± 6.9	0.26
2-	50.0 ± 25.0		50.0 ± 25.0	

OS = overall survival, PFS = progression free survival, HCC = hepatic cell carcinoma, AFP = α-fetoprotein, PIVKA = protein induced by vitamin K absence or antagonist, PR = partial response, CR = complete response, NC = no change, PD = progressive disease.

Treatment

For treatment planning, abdominal pressure corsets such as a body shell (19 cases) and vacuum cushion (59 cases) such as blue back (5 cases), Vac-Lok (13 cases), or Body-Fix (5 cases) were used. In one case, none was used. Tumor motion was confirmed at < 1 cm in the cases using abdominal pressure. The gross tumor volume was delineated on both inspiratory and expiratory planning CT images by the respiratory depression method. The breath-holding method was used in 43 cases, the gating method in 10 cases, and the respiratory depression method in 25 cases. One patient was treated with free-breathing. The planning target volume was configured considering respiratory movement, the set-up margin, and the sub-clinical margin. SBRT was performed with an X-ray beam linear accelerator of 6 MV. The total irradiation dose delivered was dependent on the judgment rendered at each institution. A collapsed cone convolution, superposition algorithm, or analytical anisotropic algorithm was used for dose calculations.

The mode value of the total irradiation dose was 48 Gy in 4 fractions (38/79 cases) (from 40 Gy in 4 fractions to 60 Gy in 10 fractions). The prescription point was D95 (dose covering 95% volume within the PTV) in 48 patients (61%) and the iso-center in 31 patients (39%). The biologically effective dose (BED) ($\alpha/\beta = 10$ Gy) was 75–106 Gy (median: 96 Gy) (Table 1). The following formula for BED_{10} was used: BED (Gy_{10}) = $nd \times (1 + d/10)$. In all cases, CT registration such as kV cone beam CT or on-rail CT was performed during each treatment.

SBRT was delivered using multiple non-coplanar static beams (using >7 non-coplanar beams) generated by a linear accelerator or volumetric-modulated arc therapy. Daily image guidance, by using either orthogonal X-rays or onboard CT imaging, was used to re-localize the target before treatment delivery.

In seven patients, TACE was performed before SBRT. Oral tegafur/CDHP/oteracil potassium (S-1) was combined concurrently with liver SBRT in one patient.

Follow-up

Patients were examined every 1 to 3 months for 1 year after liver SBRT and tri-monthly thereafter. Laboratory tests were performed at every visit. Treatment responses and intrahepatic recurrences were evaluated with dynamic contrast-enhanced CT or MRI every 3 months according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [16]. Toxicity was evaluated with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Acute and sub-acute toxicities were defined as adverse events occurring within 3 months and 3 to 6 months, respectively, after liver SBRT. Late toxicities related to liver and other toxicities were defined as those occurring after 6 to 12 months and from 6 months to the last follow-up, respectively. Laboratory tests included determinations of aspartate aminotransferase, total bilirubin, platelet count, and albumin.

Statistical analysis

Survival rates were calculated by Kaplan–Meier analysis. Log-rank testing was used to compare outcomes between the subsets of patients analyzed. Cox proportional hazards regression analysis was used for multivariate analysis. A *P*-value of < 0.05 was considered significant. Data were analyzed with SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). The points on survival curves by Kaplan–Meier were censored cases.

RESULTS

Eligible patients

The median follow-up time was 21.0 months (range, 3.4–68.3 months) for surviving patients. SBRT was performed as scheduled and was feasible in all patients. At the last follow-up, 48 cases (61%) had survived and 31 cases (39%) were deceased.

Treatment outcomes

The first local effect was complete response in 36 cases (46%), partial response in 28 cases (35%), no change in 9 cases (11%), progressive disease in 4 cases (5%), and not evaluable in 2 cases (3%). At censoring during the follow-up, 14 cases (18%) had local progression, 63 cases (80%) did not have local progression, and 2 cases (3%) were not evaluable.

For the 79 patients, the 2-year overall survival (OS), progression-free survival (PFS), and distant metastatic-free survival (DMF) were 52.9% ± 7.1%, 39.9% ± 6.9%, and 76.3% ± 6.6%, respectively. The number of patients at risk was 43 (54%), 21 (27%), 9 (11%), and 3 (4%) at 1-, 2-, 3- and 4-years in OS, respectively.

The results of sub-analysis of survival are shown in Table 2. Sex (female vs male) and serum PIVKA-II value (over 35 vs under 35)

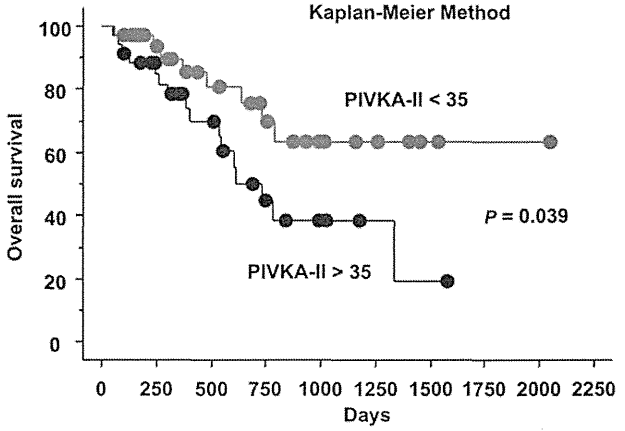

Fig. 1. Overall survival curves by serum PIVKA-II value (over 35 vs under 35 AU/ml). There was no patient with serum PIVKA-II level of just 35 AU/ml.

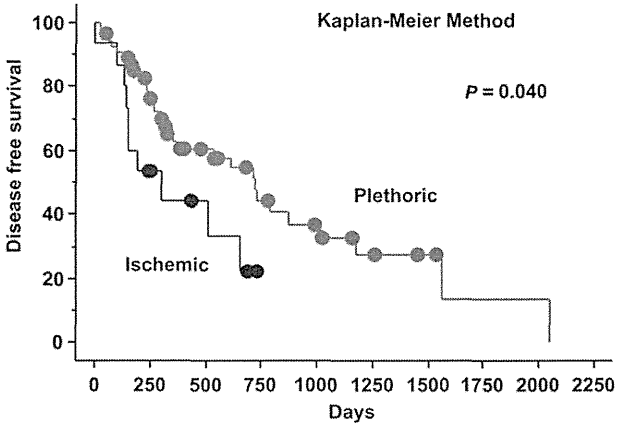

Fig. 2. Progression-free survival curves by HCC type (hypovascular vs hypervascular).

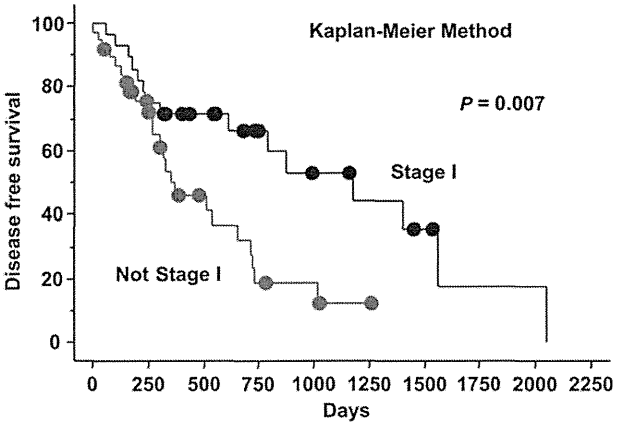

Fig. 3. Progression-free survival curves by clinical stage (I vs II–III).

Table 3. Multivariate analysis for survival

Factors	OS		PFS	
	P-value	95% CI	*P*-value	95% CI
Stage	0.47		0.017	
I		0.303–1.730		0.190–0.848
II–		1		1
Sex	0.29		0.36	
Male		1		1
Female		0.123–1.871		0.246–1.665
PIVKA-II	0.28		0.56	
Over 35		0.656–4.330		0.604–2.547
Under 35		1		1

OS = overall survival, PFS = progression free survival.

(Fig. 1) were significant predictive factors for 2-year OS ($P = 0.044$ and 0.039, respectively) by the log-rank test. HCC type (hypovascular vs hypervascular) (Fig. 2), sex (female vs male), and clinical stage (I vs II–III) (Fig. 3) were significant predictive factors for 2-year PFS ($P = 0.040$, 0.049 and 0.007, respectively) by the log-rank test.

By multivariate analysis (Cox proportional hazards regression analysis), clinical Stage I vs II–III (other covariates were male vs female and PIVKA-II > 35 vs < 35) was the only significant predictive factor for PFS ($P = 0.017$, 95% CI = 0.190–0.848) (Table 3). No differences in predictive factors were shown for OS and PFS, even when other factors such as tumor diameter ≥30 mm vs <30 mm, hypervascular vs hypovascular HCC by CT scan, and BED_{10} ≥100 Gy vs <100 Gy were added to the analysis.

Treatment-related toxicity

All liver SBRTs were completed without toxicity during the RT period. There was no Grade 5 toxicity. After the RT period, six patients (4.6%) experienced Grade 3–4 gastrointestinal toxicity and three patients (2.3%) had Grade 2 gastrointestinal toxicity. With regard to Grade 3–4 toxicities, duodenal ulcer, transverse colon ulcer, gastroduodenal aorta rupture, biliary stricture after SBRT occurred in one patient, respectively, and gastrointestinal bleeding in two patients. Only the gastroduodenal aorta rupture was Grade 4 toxicity. Of these nine patients, seven had a Child–Pugh score of Grade A, and the other two patients had a Child–Pugh score of Grade B before SBRT. No significant (≥ Grade 3) liver enzyme elevation was observed during treatment, nor was classic RILD observed.

DISCUSSION

This is a retrospective study that reviewed data extracted from the database of JRS-SBRTSG for 79 patients with HCC treated at six institutions. The OS of 53% in this study at 2 years after liver SBRT might be considered satisfactory considering that the patient group included frail patients for whom surgery was contraindicated due to

Table 4. Previous reports on survival after SBRT for HCC

Year	Ref	Dose	Subject	*n*	MST (mo)	OS	PFS	Median size	Child
2008	[17]	Median 36 Gy/6 Fr	HCC	31	11.7	1 year: 48%		173 cm^3	
2010	[18]	Median 36 Gy/3 Fr	HCC	17		1 year: 75%			
						2 year: 60%			
2010	[19]	30–39 Gy	HCC	42		1 year: 93%	1 year: 72%	15.4 cm^3	
						3 year: 59%	3 year: 68%		
			HCC	25		1 year: 79%		4.5 cm	A: 48%
2010	[16]	45 Gy/3 Fr by Cyber				2 year: 52%			B: 4%
									C: 28%
2011	[20]	Median 44 Gy/3 Fr		60		2 year: 67%	2 year: 48%	3.2 cm	A: 60%
									B: 40%
2012	[21]	Median 30 Gy/15 Fr	HCC	21		1 year: 87%			
			ICC	11		2 year: 55%			
2013	[15]	Median 36 Gy/6 Fr	HCC	102	17.0	1 year: 55%		117 cm^3	A: 100%
						2 year: 34%			
2013	[22]	Median 60 Gy	HCC	14	37.0	1 year: 83%			
						2 year: 83%	2 year: 54%	2.3 cm	

MST = median survival time, OS = overall survival, PFS = progression-free survival, Child = Child–Pugh Grade.

decompensated cirrhosis and who were in an older age group (median age 73 years). Patients in this study were very heterogeneous, and some patients might not have been candidates for SBRT according to strict guidelines. Survival data was the only factor analyzed in this study.

Survival data after SBRT for liver tumor from previous reports are summarized in Table 4. According to those reports, the 2-year OS was 34% [15], 52% [16], 55% [21], 60% [18], 67% [20] and 83% [19]. The 2-year OS was 53% in the present study, which cannot be viewed as a satisfactory result. In order to improve our results for survival, an increase in the radiation dose may be required, although BED_{10} was not the factor for survival in the present study (Table 2). The median BED_{10} in this study was 96 Gy; therefore, over half of the patients received a BED_{10} of <100 Gy. Dose escalation for HCC patients with decompensated cirrhotic liver disease may be deleterious with respect to normal liver tolerance. Takeda *et al.* [23] used 35–40 Gy in five fractions (59.5–72.0 Gy in BED_{10}), based on baseline liver function and on liver volume receiving ≥20 Gy (V20) in SBRT for untreated solitary HCC patients. They reported relatively good results, in which the 2-year local control rate and OS were 95% and 87%, respectively [23], although the BED_{10} was not very high. In their paper [23], the doses were prescribed to the planning target volume surface. In the present study, on the other hand, the doses were prescribed to the PTV-D95 (61%) or the iso-center (39%).

By multivariate analysis, clinical Stage I vs Stage II–III was the only significant prognostic factor for PFS. The main prognostic factors of HCC reported previously included stage classification, invasion to a blood vessel, liver function, tumor diameter, or the number of tumors [24–26]. However, in our study, clinical stage was found to be the sole prognostic factor.

Guidelines for HCC diagnosis indicate that a pathological diagnosis is not necessary if a tumor has a typical radiographic appearance. In this study, 20% of the patients had hypovascular HCC, and most of these HCC lesions were diagnosed by ^{18}fluorine-fluorodeoxyglucose positron-emission tomography study and the α-fetoprotein tumor marker of the L3 fraction. The reason for the poorer survival of patients with the hypovascular type of HCC than patients with the hypervascular type was not clear. Usually, hypovascular HCC is at an earlier stage and has a good prognosis. This reason why hypovascular HCC had a poorer prognosis may be that many cases of hypovascular HCC in this study had been observed without immediate treatment until size-up, plethoric change, and/or MRI signal change, as stated above.

Only one patient with Child–Pugh Grade C was treated with SBRT in this study. In that patient, there was no other treatment option, and the patient was informed of the risks of the procedure and provided consent.

There are some limitations in this study in that it is retrospective and part of a multi-institutional series with a relatively short follow-up period (median 15 months). In addition, the irradiation dose and follow-up methods were inconsistent. The reason for the lack of difference according to the stratification of the irradiation dose may be due to the various algorithms or to the differing prescription points between institutions.

CONCLUSION

Overall survival after SBRT for liver tumor was satisfactory, especially in Stage I HCC, despite the candidates being unsuitable for resection and ablation. SBRT is safe and might be an alternative method to resection and ablation.

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施設の成長と歩みをともにするための放射線治療の現状と課題

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要旨：近年の放射線治療は、照射患者数の増加と診療報酬の上昇によって優良収益部門になり、また先端機械工学を応用した高精度照射装置の導入による広告的効果も併せ持ち、多くの医療施設において経営戦略上の投資対象となっている。今後、継続的な放射線治療施設の全体と照射現場の歩調を合わせた成長のためには、装置やスタッフのセンター化・放射線治療専門医やがん放射線療法認定看護師の育成・外来部門の充実・照射技術別の適切な適応判断に基づいた運用・院内各他科や他院との連携・画像診断医との協力などが重要である。

2人に1人がんを経験し、そのうちの半分以上に放射線治療が行われる。すなわち放射線治療は全国民の4人に1人以上が経験する基本医療である。よって、全ての診療科とその医師にとって、放射線治療医と良好な関係を保つことが重要である。

近年の放射線治療の診療報酬は、2年ごとの改定で着実に増点と新規技術の保険収載がなされてきた。その理由は、放射線治療の技術進歩とともに、より低侵襲で高い抗腫瘍効果が得られるようになり、がん診療における放射線治療の役割が見直されると同時に、放射線治療患者数の著明な増加が背景にあり、厚生労働省が放射線治療界を発展させようとする政策があったからである。

放射線治療は、病院収入的に一昔前のお荷物的存在から優良黒字部門に急激に変化し、病院の発展のために放射線治療部門の充実に投資する施設が増えたのは間違いない。

本稿では、これからの放射線治療現場と所有施設の共同発展のために、現状を分析し課題について考えてみたい。

放射線治療環境の現況

①患者数

日本ではがん罹患患者の約4分の1に放射線治療が施行されているが、近年急速に増加しており、将来的には欧米並みの2分の1から3分の2までに達する可能性も予想されている。これは、放射線治療の技術進歩による根治率の向上、高齢化とQOL重視志向による低侵襲治療の選択などによる影響が考えられるが、元々放射線治療ががん診療において果たすべき本来の役割がようやく適切に理解されつつあることが大きいと思われる。

手島・滝崎らによる日本放射線腫瘍学会の構造調査結果に基づく年間の放射線治療患者数によると、2010年までは急上昇を示しているが、10年、11年とほぼ横ばいであり、推定増加曲線を下回る傾向が見られている（図1）。この原因としては、放射線治療医数が患者増に追いつかず、患者数を制限せざるを得ない状況にある可能性や、分子標的製剤や緩和ケアの発達により転移性がんの放射線治療の紹介が以前より減少している可能性などが考えられる。

また、高齢化と同時に人口減少が加速度的に進んでいる日本では、いずれがん罹患患者数の減少も来すことが予測され、放射線治療患者数の今後の動向は施設運営上も注視が必

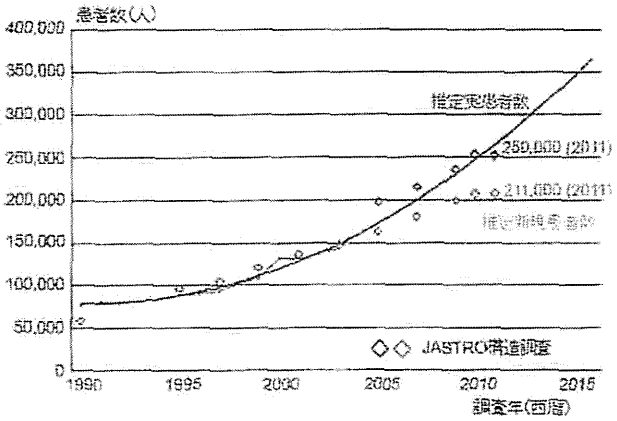

図1　年間の放射線治療患者数（新規・実数）と2008年の時点での将来予測曲線
（日本放射線腫瘍学会構造調査結果）（手島昭樹先生、沼崎穂高先生のご厚意による）

要であり、放射線治療の環境をより整えるとともに、有効性をより向上させ、内外に向けてアピールすることが重要になるであろう。

②スタッフ

日本の放射線治療は、構造的な基準を十分に満たさずにスタッフは複雑かつ多忙な業務に追われている施設が多いと言われてきた。10年後の放射線治療患者数を40万人とした場合の必要とされる放射線治療に携わるスタッフ数の予測と実数は表1の通りであり、10年の時点ではどのスタッフ職種も非常に少ない状況であったが、その後の5年間で十分とは言えないまでも急速に充足されていることが分かる。

また、国が指定したがん診療連携拠点病院・地域がん診療病院・特定領域がん診療連携拠点病院の「422施設」の情報[3]によると、これらの中で放射線治療を実施している409施設のうち、専従の医学物理士・品質管理士がいる施設割合は72・6%、専従または専任の技術者として医学物理士を配置している施設割合は48・9%、専従または専任の技術者として品質管理士を配置している施設割合は23・7%であり、十分とは言えないが徐々に充足されていることが分かる。これは放射線治療の将来性への期待の表れだと思われるが、医学物理士や放射線治療品質管理士の職制や雇用枠は未だ十分に整備されていない。

また、放射線治療専門医数については将来的に2倍に増加させる必要があり、早急な育成は文科省・厚労省・各大学・学会の重要な課題である。照射装置所有施設において、放射線治療医師の常勤によって病院全体のがん治療成績が向上することが、手島らの調査[2]で判明しており（図2）、放射線治療施設において常勤放射線治療専門医を常勤化させることは最も重要である。

さらに、がん放射線療法認定看護師につい

表1　10年後に必要な照射関係スタッフ数の予測と現在の人数
（10年後の放射線治療患者数を40万人として計算）

職種	10年後に必要な人数	2010年の人数	2015年の人数
放射線治療専門医（日本放射線腫瘍学会・日本医学放射線学会共同認定）	2000人（1人当たりの患者数年間200人として）	約600	約1000
放射線品質管理士	1333人（1施設の年間照射患者数300人として）	593	1116
医学物理士	667人（2施設に1人必要として）	488	861
放射線治療専門技師	2666人以上（治療装置1台に2名以上として）	809	1527
がん放射線療法認定看護師	667人（2施設に1人必要として）	不明	200

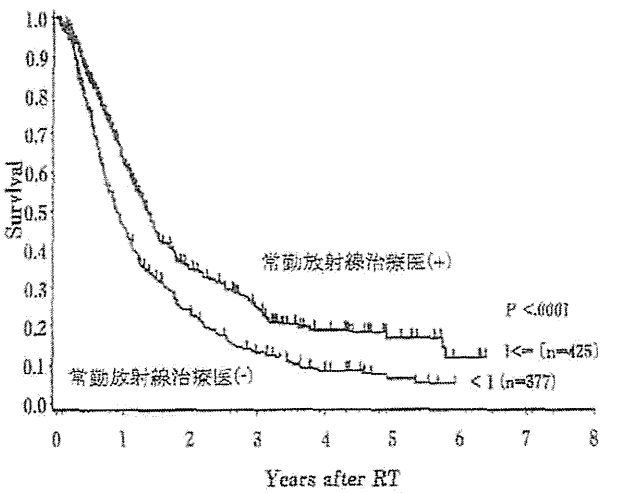

図2　放射線治療装置所有施設における常勤放射線治療医の有無による非小細胞肺癌治療成績の比較[2]

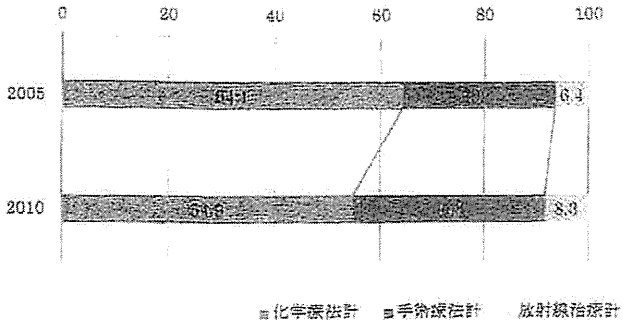

図４　がん医療費に占める化学療法、手術、放射線治療の比率の変化（「国民医療費の概況」報告書と「社会医療診療行為」の調査データより推計、土器屋卓志先生のご厚意による）

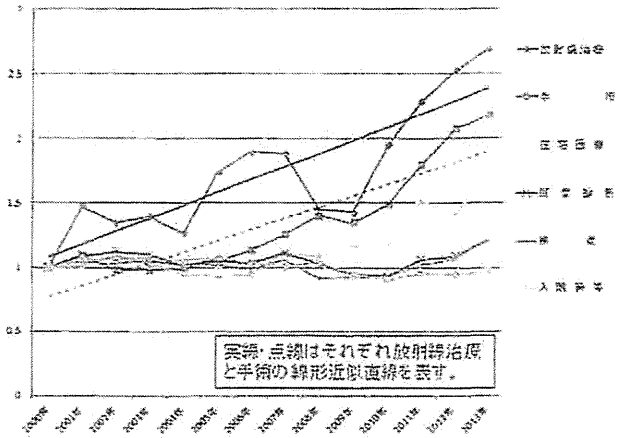

図３　代表的な医療行為別医療費の増減率（2000年＝1）（社会医療診療行為別調査　６月の実績より）（土器屋卓志先生のご厚意による）

表２　照射技術別の年間医療費（芦野靖夫様のご厚意による）

Linacに支払われた年間の診療報酬総額： （単位：百万円）	2010年	2011年	2012年	2013年
従来型放射線治療に支払われた診療報酬総額	¥60,936	¥71,597	¥77,003	¥79,201
①　1門または2門照射に支払われた診療報酬総額	¥10,782	¥14,402	¥14,412	¥14,056
②　非対向2門または3門照射に支払われた診療報酬総額	¥21,398	¥23,777	¥25,189	¥25,214
③　4門以上、運動または原体照射に支払われた診療報酬総額	¥28,756	¥33,418	¥37,402	¥39,931
強度変調放射線治療に支払われた診療報酬総額	¥8,411	¥8,591	¥12,558	¥15,574
定位放射線治療に支払われた診療報酬総額	¥7,569	¥8,857	¥8,368	¥9,454

ても、研修施設の運営の困難さや看護協会内での位置づけなど課題も多く、今後の育成に不安が残っている。がん放射線療法認定看護師は、がん診療連携拠点病院の施設基準や外来放射線照射診療料における加算要望の点でも重要であり、今後の適正な育成環境の整備が急務である。

③放射線治療の診療報酬

新規の放射線治療技術に対する診療報酬は、04年の直線加速器による体幹部への定位放射線治療、08年の強度変調放射線治療、10年の画像誘導放射線治療、12年の呼吸移動対策など、矢継ぎ早に評価されてきた。

放射線治療の年間医療費は、90年→03年→13年で、2066億円→4586億円→1176億円と、全体的な診療報酬が抑制されている中で、特筆すべき伸び率を示してきた。

その背景には、日進月歩の技術進歩や放射線治療患者数の激増があり、放射線治療へ評価に将来的な発展の期待が上乗せになっている表れであろう。また、00年以降の放射線治療・手術・在宅医療・画像診断・検査・入院料についての相対伸び率を図3に示すが、ここでも放射線治療の相対伸び率の大きさが目立っていることが分かる。

図4に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を示す。05年から10年間の占有率の変化は、化学療法はマイナス14%に対して、手術はプラス25%、放射線治療はプラス30%であり、相対的占有率は放射線治療が最も伸びていることが分かる。

また、表2は10年以降の放射線治療に支払われた年間医療費を照射技術別に示したものである。強度変調放射線治療や定位放射線治療の伸び率が、従来型放射線治療に比べて大きいことが如実に分かる。

以上から明らかにされたように、放射線治療の診療報酬は医療界の中でも最も成長部門であり、特に先端的高精度放射線治療を中心にすることで施設の潤沢な収益に貢献できるだけでなく、施設の看板広告的な効果も大きくなるため、高精度放射線治療に特化した民間施設が次々に増えつつある。

しかし、この現象は不必要に高利益型の放射線治療への不当な誘導を生まないとも言えない。限られた施設の一時的な発展のために放射線治療界全体の衰退を引き起こさないように、メーカや販売業者側も十分な注意を払う必要があるだろう。

放射線治療現場と施設の発展のために必要なこと

①照射施設の効率的配置（センター化）、放射線治療計画と照射作業の役割分担

照射機器数は全国で750台余りであり、1装置当たりの平均患者数で計算すると現状では装置数は少ないとは言えないが、問題は実際の1装置当たりの照射患者数に大きなばらつきがあるという実態である。約1／4の照射装置が常勤放射線治療医の不在な施設に配備されており、そのような施設では必然的に照射患者数が少ない。照射施設の適正な配置（センター化）が必要であり、すなわち常勤放射線治療医のいる施設への集中化とセンター的施設への放射線治療医の配備が必要に

なる。保険診療報酬上もがん診療拠点病院の施設基準からも照射施設の集中化が促される仕組みになっている。

一方で、センター的照射施設の放射線治療医への患者集中が生じるので、放射線治療上の役割における放射線技師・品質管理士・医学物理士の関わる範疇を可及的に拡大していく必要がある。そのためにも、放射線技師・品質管理士・医学物理士の職制役割分担を整備することは急務であり、その上でこれらのスタッフを増員していくことが解決策として近道であろう。

②放射線治療外来のスタッフ（放射線治療専門看護師を含む）の充足とアメニティの整備

図5に放射線治療患者の外来比率を示すが、着実に増加していることが分かる。12年改定以降は外来放射線照射診療料が設定され、またより早期で状態のよい症例が増えることにより、今後もさらに外来比率が増加していくだろう。したがって、放射線治療を受けている患者数の約半分を占める外来通院患者に対する加算に見合った対応を準備する必要がある。

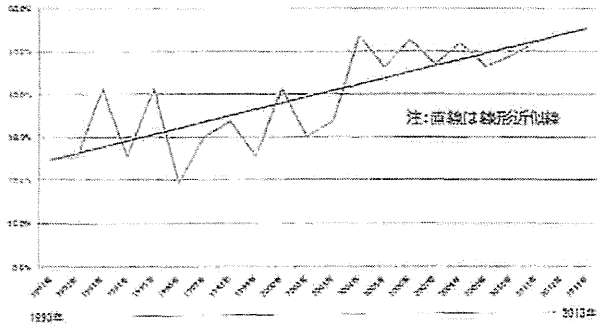

図5 「放射線治療患者の外来比率」 社会医療診療行為別調査（各年6月実績）より作成
（土器屋卓志先生のご厚意による）

ただでさえ、外来通院の場合待ち時間を強要される場合も少なくないので、待ち時間を快適に過ごせる待合室の整備や、患者の状態に細かく対応できる専従看護師の育成・配属が望ましい。

③放射線治療施設の発展のための秘策―他科・他施設・画像診断部門との symbiosis partnership

・院内での連携―内科系・外科系との集学的治療

手術は術前・術後照射と組み合わされることが多く、また化学療法も放射線治療と併用されることが多いので、がん治療に携わる外科医・内科医にとって、施設内で放射線治療が可能であることは基本的重要条件である（優秀な外科医・内科医ほど、放射線治療のできない施設には行きたがらない）。

・他施設との連携―セカンドオピニオンとしての役割

放射線治療医は根治と緩和の両方の視点・全身的な判断・多種類のがんに対する包括的判断・手術や化学療法との比較・他施設との技術の相違、などの点において最も豊富な知識や経験を持ち得る環境の中にあるため、がん治療におけるセカンドオピニオンを受ける場としても最適であると思われる。放射線治療部門を持たない他施設からのコンサルトを密に受けることによって、他院とのより機能的な連携の強化につながり、放射線治療患者数の増加にも結びつくであろう。

・画像診断部門との連携

放射線治療医にとって画像医学の学習は常に必要であり、画像診断医にとってもオンコロジーの基本を学び、その視点から画像を眺めるようになるためには、放射線治療を学ぶことがその一番の近道である（曽根先生からの依頼原稿）。

放射線治療の重要性が増す中で、放射線治療の適応や照射後の変化を放射線治療医と画像診断医で常日頃意見交換しておくことは、それぞれの教育的価値も高い上に、施設の発展に大きく寄与すると考える。

最近のニュースに接し私が確信したこと

本稿作成中に大きなニュースが2つあった。1つは、山梨大学出身の大村 智氏のノーベル医学生理学賞の受賞である。大村氏は開発した治療薬の人への使用を無償で許可し、その名言「人の役に立つことだけを考えてきた」は、大村氏の研究哲学として繰り返し報道された。一切の特許を取得せず、第1回ノーベル物理学賞の賞金さえ寄付した偉大なるレントゲン博士の「科学とは人民に貢献してこそ科学である」という言葉を思い出させる。何事も、継続的な発展を来すためには「人と社会に寄与する」ための高い理想に支えられた哲学が必要である。

そしてもう1つは「日本の年間医療費が40兆円を超えた」ことである。国民1人当たり年間に30万円以上も医療費を使用している訳だ。筆者は原稿締め切りに追われながらこれらのニュースを目にし、「放射線治療と施設の継続的な発展のためには、患者さんの役に立つと同時に医療費の抑制につながることを常に考え、ぶれずに誠実に続けていくことが重要である」ことを確信した次第である。

本稿での要点

本稿で述べた要点をまとめておく。

・放射線治療は、収益的にも対外的アピール度としても施設の中で重要な役割を果たしている。

・放射線治療全体の医療費の伸びは急速であり、特に高精度照射技術において顕著である。

・放射線治療患者数は、上昇一辺倒からやや伸び率が鈍化している可能性がある。

・医学物理士や放射線治療品質管理士の増加は目覚ましく、現場での充足率も向上してきているため、診療報酬の伸びによる利益が治療現場の質の担保に還元されている状況が見られる。

・今後、さらなる放射線治療施設の発展のためには、装置やスタッフのセンター化・放射線治療専門医やがん放射線療法認定看護師の育成・外来部門の充実・照射技術別の適切な適応判断に基づいた運用・院内各他科や他院との連携・画像診断医との協力などが重要である。

謝辞

本稿において、データの分析・提供・ご指導に多大なご支援をいただきました、杏雲堂病院の土器屋卓志先生・大阪成人病センターの手島昭樹先生・大阪大学の沼崎穂高先生・東京ベイ先端医療・幕張クリニック幕張放射線クリニックの遠山尚紀先生・エレクタ株式会社の芦野靖夫様・東京女子医大の唐澤久美子先生に心から感謝いたします。

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※ ※

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」「早期の癌治療の選択」「エビデンス放射線治療」「放射線腫瘍学」など。

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Development of Clinical Database System Specialized for Heavy Particle Therapy

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Abstract

We have developed a data archiving system for study of charged particle therapy. We required a data-relation mechanism between electronic medical record system (EMR) and database system, because it needs to ensure the information consistency. This paper presents the investigation results of these techniques. The standards in the medical informatics field that we focus on are Integrating the Healthcare Enterprise (IHE) and 2) Health Level-7 (HL7) to archive the data. As a main cooperation function, we adapt 2 integration profiles of IHE as follows, 1) Patient Administration Management (PAM) Profile of IHE-ITI domain for patient demographic information reconciliation, 2) Enterprise Schedule Integration(ESI) profile of IHE-Radiation Oncology domain for order management between EMR and treatment management system(TMS). We also use HL7 Ver2.5 messages for exchanging the follow-up data and result of laboratory test. In the future, by implementation of this system cooperation, we will be able to ensure interoperability in the event of the EMR update.

Keywords:
Radiotherapy, Database, Strandards, IHE, HL7.

Introduction/Purpose

Our hospital has a mission of clinical research for radiotherapy. Charged particle therapy (carbon ion) was started in 1994, and over 9,500 cases have been treated by November, 2014. To accomplish this mission, we managed multi-system such as electronic medical record systems (EMR) and charged particle therapy treatment management system (TMS).

In 2000, we started to operate the Advanced Medical Information Database System (AMIDAS) for archiving the radiotherapy information. With the starting of EMR, we allocated a role to information systems as follows, EMR: input data related radiotherapy, AMIDAS: make report and summary of radiotherapy. So the AMIDAS is required to construct a mechanism to collect the data which is input by end-user on EMR.

Methods

The data targeted for the cooperation are following: (1) patient demographic information, (2) tumor related information, (3) radiation plan information, (4) follow-up information (tumor effect, advance reaction, mortality, etc.), (5) laboratory results, (6) treatment delivery information. We divided the implementation process into two stages and examined it as two steps: (1) investigated the availability of IHE [1]. (2) investigated the use of HL7 messages.

Results

This cooperation function was realized by two IHE integration profiles as follows, (1) Patient demographics and visit information: PAM Integration Profile, (2) Radiotherapy order and delivery information: ESI Integration Profile. For communication of treatment follow-up information and laboratory test we defined context and used HL7 messages.

Discussion

We show the comparison results using standard with original sysytem-interface in Table 1.

Table 1– The Comparison of Standard with original messages

Comparisonpoint	Standard-IHE	Standard-HL7	Orignal interface
Meeting number of times	little	few	much
The use of the library	possible	possible	impossible
Time to make specifications	short	middle	long

Conclusion

In comparison with original message system interface, it may be said that the system which was developed using a standardization technology has interoperability. From the standpoint of system-operation by using standards, when we will renew the EMR, AMIDAS can receive the data from EMR without software modification.

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[1] IHE(Integrating the Healthcare Enterprise) http://www.ihe.net/Technical_Frameworks/

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放射線治療病歴データベースシステムにおけるデータスキーマの検討

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Examination of the data schema for Radiotherapy database

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抄録：当院では、放射線治療に関するデータの相互運用性確保を目的に、2000 年に放射線治療病歴データベースシステム(AMIDAS)の運用を開始した。今回、当該システムの更新計画のため、稼働時に設計したデータの生成状況を調査し、この情報をベースに第 II 期 AMIDAS のデータ構造（スキーマ）を検討した。過去10年間のデータテーブルとしては、198/426（46%）が利用されていないことがわかった。また、他システムとの連携運用が開始することによりデータ充足度が高まることも観察された。取得した情報を基にテーブルおよび項目を約2／3にすることができた。今回の作業により、データ構造がシンプルとなりデータ抽出などが簡易に行える基礎が構築できた。このことにより、行政機関や学術団体、学会、臨床研究会等に提出する登録情報の抽出がより容易になることが期待できる。

キーワード： Radiotherapy, Database, Schema, Oncology database

1. はじめに

当院は、ベッド数 100 床, 外来患者数は 70～100 人/日の放射線科単科の病院である。診療は放射線治療に特化しており、1961 年に X 線等による放射線治療を開始し、1994 年より炭素イオン線を用いた悪性腫瘍に対する放射線治療を開始し、2014 年 12 月までに約 9,800 例の治療を行っている。また当院は放射線に関する研究機関でもあり、これらの放射線治療に関する疾患情報、治療内容、予後の情報は臨床研究のための重要な情報である。放射線治療に関する情報を長期に渡り一貫して管理し症例報告や治療実績件数抽出などを簡易に行うことを目的に、1999 年に放射線治療病歴データベースシステム(AMIDAS: Advanced Medical Information Database System)を構築し 2000 年より運用を開始した[1]。本システムの位置づけを図1に示す。2015 年度稼働を目標にシステム更新を行うことになった。過去 10 年間の運用を踏まえ、移行すべき機能の整理および必要なデータ項目の整理を行い、新システムの構成を検討することとした。本研究では、データ構造および項目（以降、第 II 期 AMIDAS 用 Schema)の整備・検討結果について報告する。

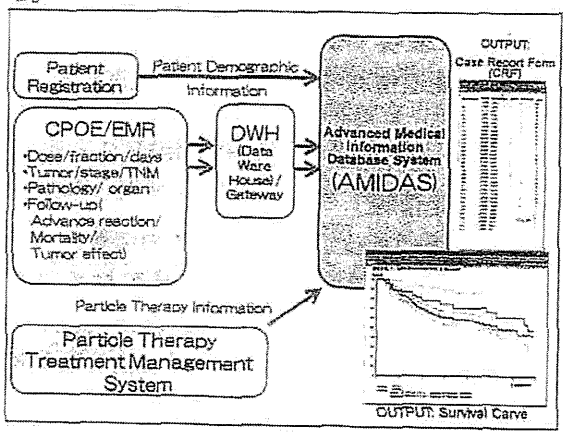

図1 医療情報システム上の AMIDAS の位置づけ

2. 方法

第 II 期 AMIDAS 用 Schema の検討にあたり次の5ステップで検討を行った。Step1)2014 年 10 月までの全てのデータ(テーブル・カラム)について、テストデータ以外の実データが格納されているものを全て洗い出す。Step2)洗い出したデータを基に利用していないテーブルおよびカラム、二重に登録されているカラムを削除した Schema 案を作成する。Step3)テーブルの Relation(親子関係)について、冗長な構造やデータ格納率を観点に精査する。Step4)利用者(医師)に、前段階までの結果を説明しコメントを反映する。Step5)放射線治療の標準データ項目 Radiation Oncology Database[2] で提案されている項目と比較・精査する。Step6)現行システムのデータベース(Schema)からのデータ移行を踏まえ、移行管理用テーブルとカラムを追加する。

3. 結果

1) データ構造検討

現行システムのデータベースは、406(うち臨床情報 150)テーブル/3,943(うち臨床情報 2,194)カラムあったものを、第 II 期 AMIDAS 用 Schema では臨床情報 100 テーブル/1185 カラムまで整理することができた。また、テーブルの Relation およびカラム位置の精査については、従来腫瘍情報として管理していた項目を治療情報(例. 腫瘍の進行状況 TNM 分類等)とする、可変登録情報となっていた項目を固定項目とする対処を行った項目(例.stage 情報、grade 情報)は 12 件であった。従来管理していない項目であったが標準データ項目と精査した結果追加した項目(例. 二次がん情報)は、11 件であった。

2) データ移行ルール検討

現行 Schema に格納されているデータを第 II 期 AMIDAS 用 Schema に移行するにあたり、ルールを検討し、次のように決めた。①患者および治療に対する情報のレベル(階層)が同一のものはそのまま移行する。②レベルが上位になった項目は、入力源は上位項目と同一であることから必ず1つに決まるため、参照キーを基に移行する。③格納データ量が少なく、検索・参照・抽出の要求もない項目については整理(削除)を行っている。これらの項目については、該当するテーブルに移行用コメント項目を設け、移行元の「項目名:値」の形式でデータ連結を行い移行する。このことにより、格納形式に差はあるが、データとしては移行前後で欠損はないこととなった。また長期間の運用における環境が都度変わっていることから、データの投入方法が統一されていない期間のイレギュラなデータについてもこの移行用コメント欄を活用することができた。

4. 今後の作業について

今回まとめた第 II 期 AMIDAS 用 Schema を基に、現行システムと過不足の無い報告書や検索・集計結果が提供できるか、レスポンスに問題ないかを観点にプロトタイプシステムを構築し、検証する予定である。また、本検討結果のうち、データ項目の削減については、過去10年間のデータ項目の利用情報の情報量を観点に、今後継続して評価を行う予定である。

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Short Communication

External effective radiation dose to workers in the restricted area of the Fukushima Daiichi Nuclear Power Plant during the third year after the Great East Japan Earthquake

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ABSTRACT

Since the Great East Japan Earthquake on 11 March 2011, Iitate Village has continued to be classified as a deliberate evacuation area, in which residents are estimated to receive an annual additional effective radiation dose of >20 mSv. Some companies still operate in Iitate Village, with a special permit from the Cabinet Office Team in Charge of Assisting the Lives of Disaster Victims. In this study, we measured the annual effective radiation dose to workers in Iitate Village from 15 January to 13 December 2013. The workers stayed in Iitate for 10 h and left the village for the remaining 14 h each working day. They worked for 5 days each week in Iitate Village, but stayed outside of the village for the remaining 2 days each week. We found that the effective radiation dose of 70% of the workers was <2 mSv, including natural radiation; the maximum dose was 3.6 mSv. We estimated the potential annual additional effective radiation dose if people returned full-time to Iitate. Our analysis supports the plan for people to return to their home village at the end of 2017.

KEYWORDS: effective radiation dose, Fukushima, ambient dose rate, decontamination

INTRODUCTION

On 11 March 2011, the Great East Japan Earthquake caused the Fukushima Daiichi Nuclear Power Plant disaster, which resulted in the release of radioactive material into the surrounding environment. Terada *et al.* pointed out that a certain amount of the ^{137}Cesium was carried by a south-east wind as a radioactive plume and precipitated over land [1]. The government designated the 20-km radius around Fukushima Daiichi Nuclear Power Plant as a restricted area and the 30-km radius as a deliberate evacuation area. Although Iitate Village is located 30 km northwest of the Fukushima Daiichi Nuclear Power Plant, the density of deposition from the radioactive material there as measured more than 1000 kBq/m^2 adjusted to 14 June 2011 [2], and a village-wide evacuation was officially announced. Maps around Fukushima showing the measured dose distribution are summarized in Fig. 1.

However, the Japanese Ministry of the Environment has permitted the continued operation of some companies and firms in Iitate, under the condition that workers are subjected to a maximum additional effective radiation dose of <20 mSv/year, excluding the natural dose [3]. Consequently, a certain number of workers have been allowed to stay in Iitate for limited hours each day, provided they commute from a place of refuge located outside of Iitate. To meet the guideline conditions for returning to the village, people in Iitate have carried out decontamination.

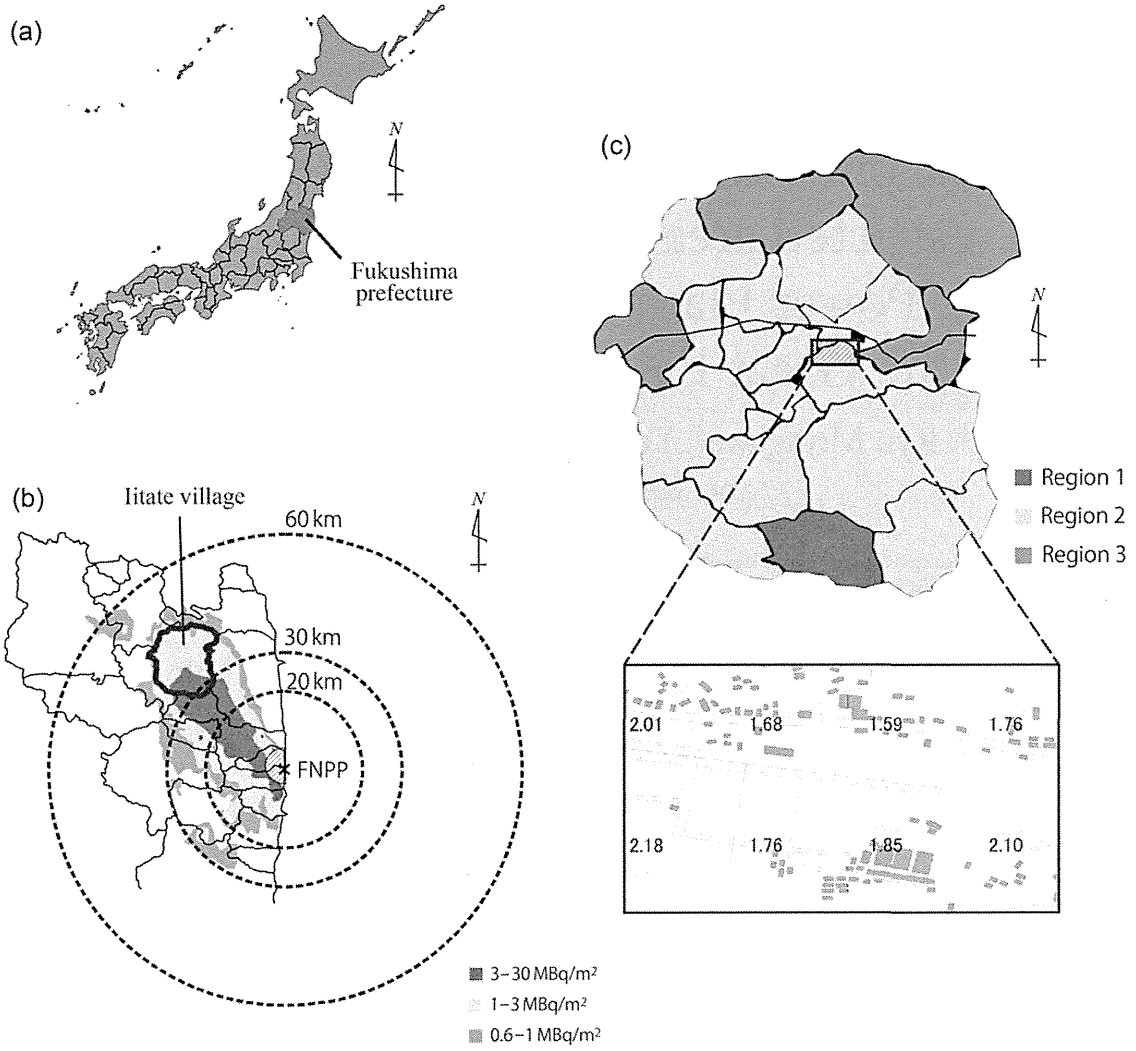

Fig. 1. Maps around Fukushima with dose distribution. (a) Location of Fukushima prefecture in Japan. (b) Cumulative dose distribution of cesium-134 and cesium-137 at ground around east side of Fukushima prefecture, which was measured by the airplane monitoring of MEXT and U.S. Department of Energy. The location of Fukushima-Daiichi nuclear power plant is shown by the point FNPP. Dose measurement is not performed for the shaded area in the vicinity of FNPP. The area surrounded by a thick line corresponds to Iitate village. (c) Areas to which evacuation orders have been issued in Iitate village, reported by Ministry of Economy, Trade and Industry [17]. Region 1 corresponds to areas where it is expected that the residents have difficulties in returning for a long time. Region 2 corresponds to areas in which the residents are not permitted to live. Region 3 corresponds to areas to which evacuation orders are ready to be lifted. The workers whose external effective radiation dose measured in this study stayed within the enlarged square area of this map for 10 h in each day. The numbers in the square area correspond to ambient dose rates [μSv/hour] measured by airborne monitor on September 2013 reported by Ref. [16].

However, direct measurement of the external exposure at Fukushima was abbreviated [4–6], and much of the data were estimated from the ambient dose rates determined by airborne monitoring [2, 7–10]. In general, the summation of the ambient dose rate is much higher than that determined by direct measurements with a semiconducting detector [4–6].

We performed direct measurements with a glass dosimeter (as is popularly used for radiation protection in laboratories and hospitals) on workers in the deliberate evacuation area. By analyzing the data, we determined the potential annual effective radiation dose for people returning to their daily lives in Iitate.

MATERIALS AND METHODS

In order to measure the effective radiation dose of workers, we used a glass dosimeter (Glass Badge: GD-450, Chiyoda Technology Corp.). This type of dosimeter is normally used to monitor the radiation exposure of a person. We asked the workers to carry the dosimeters continuously during the year (including for their commute and while

staying in their houses). We replaced the dosimeter every 2 months because the lowest detectable dose per 2 months by the glass dosimeters was 0.05 mSv, which corresponds to 0.3 mSv per year. The control glass dosimeter mostly measured the dose of natural radiation from the ground and space, which was then subtracted from the raw data. The measurement period for the estimation of the annual effective radiation dose was from 15 January to 13 December 2013 (i.e. 333 days). We recruited workers to carry the dosimeters throughout the year. We explained how to carry the dosimeter and the significance of the estimated effective radiation dose.

We recruited 64 workers (age: 19–62 years old, median: 38 years old, sex: 39 men, 25 women) in Iitate. Twenty control ambient dose monitors (in air) were employed (at 12 points indoors and eight points outdoors) at a certain facility in Iitate. Each point indoors was located by the window within the room. The ambient dose rate was measured with a NaI scintillator (TCS-172, Hitachi-Aroka Inc.).

The Ethics Board approved the protocol for this study.

RESULTS AND DISCUSSIONS

In this study, we measured two parameters using glass dosimeters: the ambient dose rate around the decontaminated facility and the total effective radiation dose per person.

Figure 2 shows a histogram of the annual effective radiation dose of the workers in 2013. For 70% of the workers, the annual effective radiation dose was <2 mSv. All of the workers with an effective radiation dose >3 mSv behaved similarly; they worked outdoors for almost 10 h in each working day. The maximum effective radiation dose reached 3.6 mSv; this worker worked outdoors close to a road located in the center of Iitate. The mean and median doses were 1.73 and 1.53 mSv, respectively. Figure 3 compares the human effective and ambient doses. There was a large difference between the effective human dose and the ambient dose both indoors and outdoors.

We roughly estimated the maximum annual additional effective radiation dose people will encounter when they fully return back to Iitate and their daily lives. To calculate such a maximum index, we use the maximum value for the annual effective radiation dose of 3.6 mSv/year in Fig. 2, which may correspond to the long tail of the histogram in [10]. This worker, and the others who belong to the high-dose group in Fig. 2, stayed at Iitate for almost 10 h and resided at a place of refuge outside Iitate for 14 hours in each working day; they worked for 5 days and stayed outside of the village for the residual 2 days in each week. Therefore, the annual additional effective radiation dose per year for a person staying full-time in Iitate (D_i) or staying outside of Iitate full-time (denoted by D_0) can be expressed by:

$$(3.6 - 0.54) = D_i \times \delta + D_0 \times (1 - \delta),$$

$$\delta = \frac{10[\mathrm{h}] \times 5[\mathrm{days}]}{24[\mathrm{h}] \times 7[\mathrm{days}]} \simeq 0.298.$$

where 0.54 mSv/year is the natural dose in Fukushima Prefecture measured by Chiyoda Technology Corp. [6]. δ corresponds to the fraction of dwell time in Iitate relative to one week. Then, $D_i = 9.34$ mSv/year if D_0 is set to the mean value of 0.4 mSv/year reported by Fukushima City. At its maximum, $D_i = 10.28$ mSv/year if D_0 is set to 0 mSv/year. Thus, D_i is clearly less than the Ministry condition of 20 mSv/year. Furthermore, much decontamination has been performed, and several half-lives of ^{134}Cesium (i.e. 2.06 years) have passed since 2011. Therefore, the actual potential effective radiation dose should be less. This result positively supports the planned return of people to their home village at the end of 2017. The actual decision to return should be left

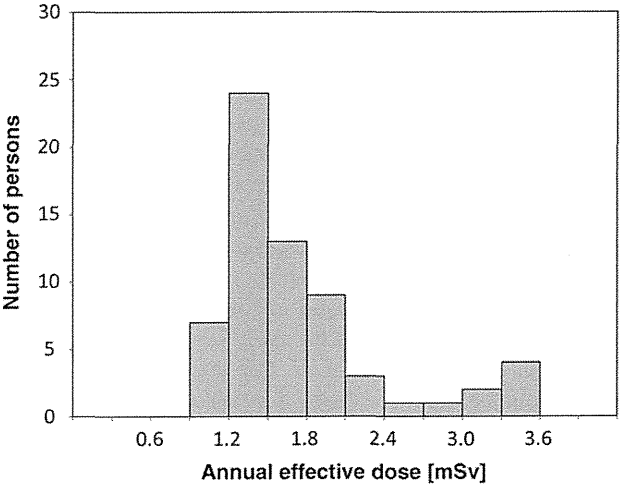

Fig. 2. Histogram of the annual effective radiation dose of 64 workers in Iitate Village for 2013. The workers stayed for 10 h of each day within the enlarged square area of Fig. 1c. We observed bipolarization of the low-dose group (showing a semi-logarithmic distribution) and the high-dose group (>3 mSv), reflecting the bipolarization of work forms; some worked mainly indoors, whereas the others worked outdoors.

Fig. 3. Comparison of the effective human dose to workers (denoted by the column 'worker') and the ambient dose in Iitate (denoted by 'indoor' and 'outdoor'). Twenty control ambient dose monitors (in air) were used (12 points indoors and eight points outdoors). Each indoor point was located by the window within a room, so the mean value indoors tended to be larger than that of workers, according to the present measurements. *P* values were calculated using the Student's *t* test.

to the people, but our results may help support their decisions and sense of well-being.

The radioactivity levels of all foods grown in Fukushima were found to be below the strict safety levels established by the Food Safety Commission of Japan, which performed strict inspections of rice and meat. The amount of internal exposure of people consuming these foods in Fukushima was less than the lower detection limit of a whole body counter (WBC) [11–14]. Therefore, most of the effective radiation dose is due to external exposure, which has not been systematically measured before. Fukushima City reported the annual exposure of people who evacuated and who were staying outside Iitate. In contrast, we measured the annual exposure of people who returned to Iitate at fixed intervals. Our data can be applied for estimation of the expected radiation dose that would be received by people who fully return to their homes and daily lives. It is unprecedented that residents return and stay in the exposure area for a certain period; this was not allowed immediately after the Chernobyl nuclear power plant accident. Therefore, our direct measurements can provide valuable data on the annual exposure likely to be experienced in the event of a nuclear disaster.

One limitation of this study is that negative feelings endemic to the afflicted people prevented us from conducting the proper behavioral survey. Now, we are following up the afflicted people with a behavioral survey in preparation for our continued research into the situation. Furthermore, Iitate does not necessarily represent the overall situation for Fukushima. By following up on the recent WHO project [16], we are planning to get comprehensive data concerning the effective radiation dose by 'D-Shuttle', together with each person's daily behavior record, which will make it possible for us to promote risk communication in Fukushima. Our recent project on time-resolved measurement and the resultant systematic risk communication will be summarized in our next report.

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INTERNAL MEDICINE

□ CASE REPORT □

Two Cases of Thymic Carcinoma Initially Presenting as Bone Metastasis: A Clinical Report and the Usefulness of CD5 Immunohistochemistry for Assessing Bone Lesions

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Abstract

Thymic carcinoma frequently spreads to the pleural space, regional lymph nodes, liver and lungs. However, an initial clinical presentation involving spinal or multiple bone metastases in patients with thymic carcinoma is extremely rare. We experienced two cases of thymic carcinoma that initially presented with spinal compression and severe pain due to multiple bone metastases, respectively. Both patients were histologically diagnosed with metastatic thymic squamous cell carcinoma based on the findings of specimens resected from the metastatic bone lesions. We herein describe the clinical courses of these cases and review the characteristics of bone metastasis of thymic carcinoma.

Key words: thymic malignancy, spinal compression, hemiparesis, chemotherapy, mediastinal tumor

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(DOI: 10.2169/internalmedicine.54.4250)

Introduction

Thymic carcinoma is a thymic epithelial neoplasm exhibiting cytological malignant features and a clinical course that tends to be much more aggressive than that of thymoma (1-4). Thymic carcinoma, located in the anterosuperior mediastinum, frequently spreads to the pleural space, regional lymph nodes, liver and lungs (1, 2). Regarding bone involvement, there are several case reports of the detection of spinal metastasis in the late phase of the clinical course in patients with thymic malignancies, including thymic carcinoid tumors (5-7). However, an initial clinical presentation with spinal or multiple bone metastases in patients with thymic carcinoma is extremely rare (8). In addition, due to the paucity of cases, there is little information about the diagnostic approach or treatment in clinical practice.

We herein describe two cases of thymic carcinoma that initially presented with spinal compression due to tumor spread into the intraductal space and severe pain due to multiple bone metastases, respectively. Both patients were diagnosed with metastatic thymic carcinoma based on the findings of immunohistochemical examinations of specimens resected from the metastatic bone lesions using a thymic carcinoma-specific marker, CD5.

Case Reports

Case 1

A 50-year-old woman presented with a three-year history of back pain. A paravertebral mass had been noticed on chest radiography and computed tomography (CT) performed during a medical examination conducted two years previously; however, the patient had not wished to undergo any further examinations. One month prior to the current ad-

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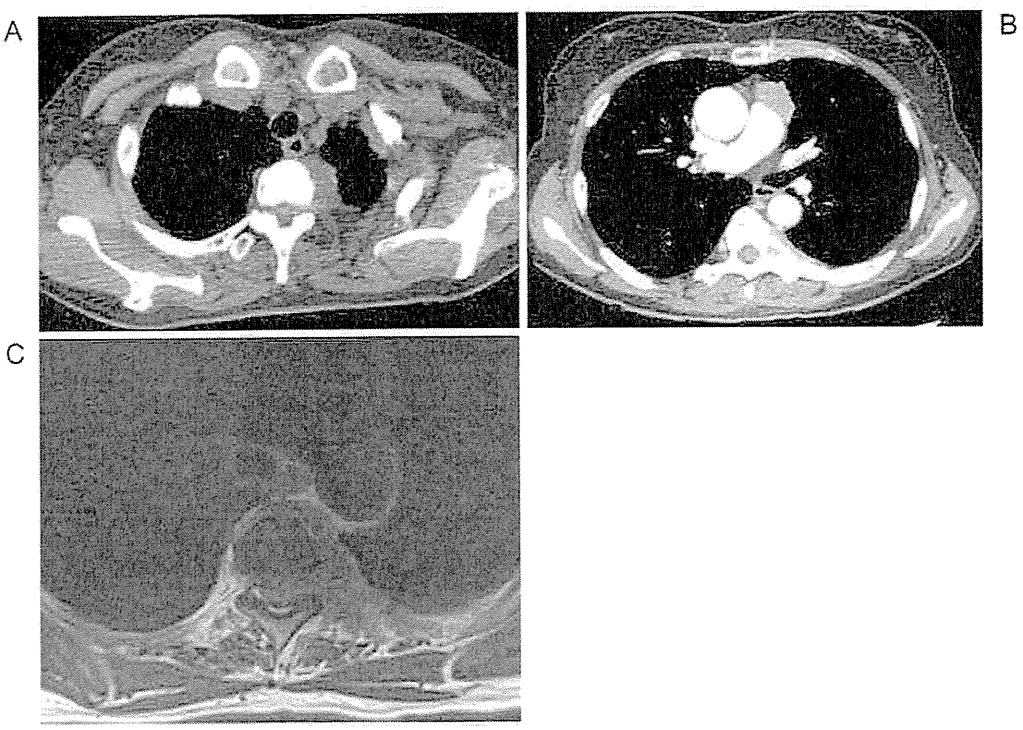

Figure 1. **Chest computed tomography demonstrated a left posterior mediastinal mass expanding along the pleura (A) and an anterior mass (B). The left posterior mediastinal mass involved the thoracic vertebra on chest magnetic resonance imaging (MRI) (C).**

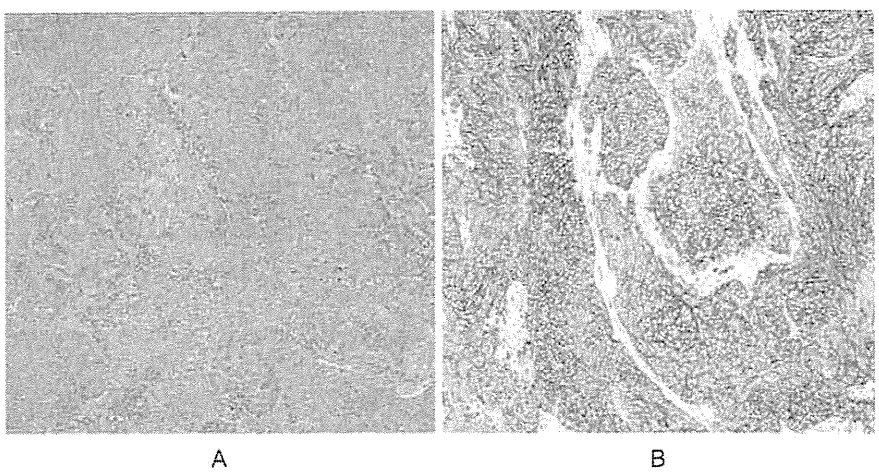

Figure 2. **The histological findings revealed squamous cell carcinoma (A). The tumor cells were positive for CD5 (B).**

mission, she developed progressive muscle weakness and numbness of the left leg. Chest CT demonstrated a left posterior mediastinal mass expanding along the pleura and an anterior mediastinal mass (Fig. 1A, B), while magnetic resonance imaging (MRI) revealed involvement of the mass in the thoracic vertebrae (Th3) (Fig. 1C). Laminectomy was performed to improve the leg paralysis, and the histopathological findings disclosed a diagnosis of squamous cell carcinoma, the tumor cells of which were positive for CD5 (Fig. 2). A tumor biopsy of the anterior mediastinum was also performed using video-assisted thoracic surgery, which pathologically confirmed the presence of thymic squamous cell carcinoma. Hence, the spinal involvement appeared to be due to direct invasion of the pleural spread of the thymic carcinoma; there were no other distant metastatic lesions. The patient therefore received chemotherapy with a combination of cisplatin (50 mg/m^2) and doxorubicin (40 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 3 and cyclophosphamide (700 mg/m^2) on day 4 [cisplatin, doxorubicin, vincristine and cyclophosphamide (ADOC) chemotherapy]. Four cycles of ADOC chemotherapy and subsequent radiotherapy for Th2-5 were performed, and the chemotherapy

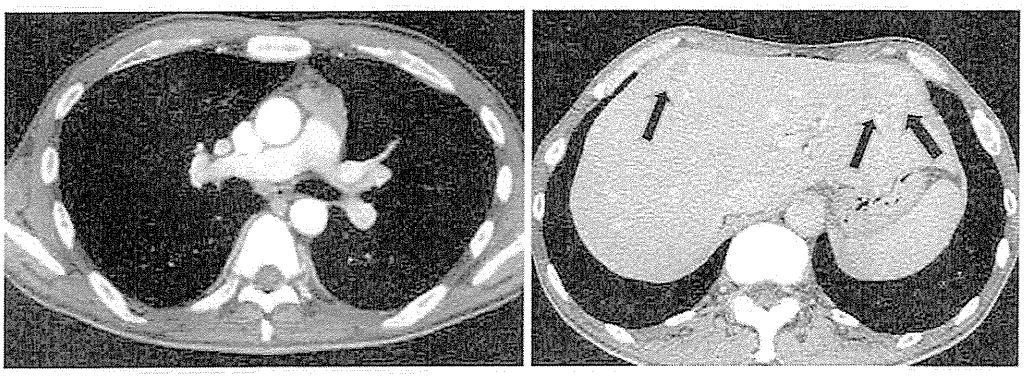

Figure 3. **Chest computed tomography showed abnormal masses in the anterior mediastinum (A) and liver (B).**

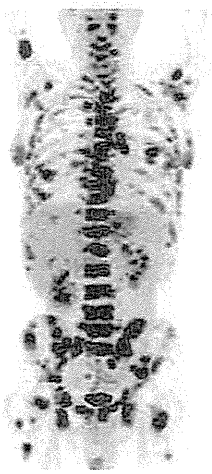

Figure 4. **^{18}F-Fluorodeoxy glucose positron emission tomography (FDG-PET) disclosed an abnormal uptake in multiple bone and lymph node lesions, including the masses in the anterior mediastinum and liver.**

and radiotherapy resulted in stable disease. Although slight right hemiparesis persisted, she has experienced no serious problems in her activities of daily living (ADLs), and she has remained well for approximately 1.5 years since the diagnosis.

Case 2

A 49-year-old man presented with a six-month history of low back pain and arthralgia. He had been admitted to a local hospital due to progressive pain. A physical examination performed at the time revealed no specific findings, although his performance status was 2 [Eastern Cooperative Oncology Group (ECOG) classification]. In addition, chest CT revealed abnormal masses in the anterior mediastinum and liver (Fig. 3), and ^{18}F-fluorodeoxy glucose positron emission tomography (FDG-PET) showed a positive uptake in multiple bone lesions, including the mediastinal and hepatic tumors (Fig. 4). A bone marrow biopsy of the ilium was subsequently performed, and the histological findings revealed squamous cell carcinoma with tumor cells positive for CD5 (Fig. 5). Morphine therapy was therefore initiated for pain, followed by the administration of ADOC chemotherapy. Although a partial response was achieved after four cycles of ADOC chemotherapy and the dose of morphine was reduced, the patient died 10 months after the initial chemotherapy due to disease progression.

Discussion

We herein described two cases of thymic carcinoma initially presenting with spinal cord compression and multiple bone metastases, respectively. According to the classification of Masaoka et al. (9), both patients had advanced disease with bone metastases (stage IVb). Neither patient had any respiratory symptoms resulting from the primary thymic carcinoma and were diagnosed based on the findings of histological specimens obtained from the metastatic bone lesions. Similar to that observed in the present cases, Liu et al. (8) described a case of thymic carcinoma in which the patient initially developed spinal metastasis and cord compression. However, the onset of initial clinical manifestations related to bone involvement is extremely rare in patients with thymic carcinoma. Therefore, clinical physicians should be aware of the possibility of initial bone involvement in this group.

Based on the database of the European Society of Thoracic Surgeons (ESTS), 47 of 229 thymic carcinomas showed recurrence after surgical intervention, among which three patients developed bone metastasis (10). In addition, Yano et al. (4) reported 30 cases of thymic carcinoma at various stages and identified one patient who developed bone metastasis during the clinical course of the tumor. Hence, bone metastasis is usually recognized parallel to disease recurrence after surgery or progression during follow-up and/or in the late stage of the disease.

However, little information is available regarding the prevalence of bone metastasis at the time of diagnosis in patients with thymic carcinoma, especially those with ad-