研究分担報告書
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肺定位放射線治療に関する研究

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研究要旨：近年の技術進歩によって、放射線を腫瘍に集中させる高精度放射線治療が実現可能になってきている。一方で、高精度放射線治療は質の高い放射線治療を患者に提供するには、その品質保証や管理が非常に重要となってくる。体幹部定位放射線治療は、日本において確立された高精度放射線治療法の一つである。本研究においては、施設訪問による調査法において、多施設共同研究プロトコール：JCOG0702 プロトコール“手術不能または高齢者手術拒否 T2N0M0 非小細胞肺癌に対する体幹部定位放射線治療第 I 相試験”における物理面での品質保証を実施する。

A．研究目的

多施設共同研究プロトコール：JCOG0702 プロトコール“手術不能または高齢者手術拒否 T2N0M0 非小細胞肺癌に対する体幹部定位放射線治療の第 I 相試験”が実施されている。JCOG0702 プロトコール実施においては、治療計画装置で扱う線量計算アルゴリズムは、水に相当する腫瘍と水の５分の１程度である肺野のような不均質物質中での計算精度が最も高いとされる、不均質物質に対応した変形カーネルを有すモデルベースの計算アルゴリズム（不均質対応モデルベース計算アルゴリズム）を利用する方向となっている。そのため、各施設で所有している治療計画装置に搭載された不均質対応モデルベース計算アルゴリズムの線量計算精度を検証し、施設間の統一性を調査する必要がある。本研究では、肺の体幹部定位放射線治療における治療計画装置の検証に適した検証システムの構築とそのシステムを利用した調査を実施し、物理面での品質を保証することである。本年度は、JCOG0702 プロトコール参加施設の内、治療装置機器の更新があった施設に対して、訪問調査による線量計算精度検証を実施し、これまでの調査結果も踏まえて、開発した線量計算精度検証システムの有用性を評価することが目的である。

B．研究方法

昨年度までの研究成果として、JCOG0702 プロトコール参加７施設（東京都立駒込病院、山梨大学医学部付属病院、先端医療センター、東北大学医学部付属病院、北海道大学医学部付属病院、九州大学医学部付属病院、京都大学医学部附属病院）において、体幹部定位放射線治療で利用する放射線治療装置及び治療計画装置の線量精度管理に対する施設訪問調査を実施した。また、放射線発生装置の機器更新のあった先端医療センターの訪問調査を実施した。

線量計算精度の検証として、これまでに種々の肺の模擬ファントムが製作され、利用されてきた。しかし、腫瘍内のポイント線量及び肺野内での多面での線量分布を包括的に正確に測定でき、なおかつ、簡易に取り扱いが可能なファントムは無いに等しい状況であった。本訪問調査においては、水タンク式不均質肺ファントムを製作して用いた（図１参照）。

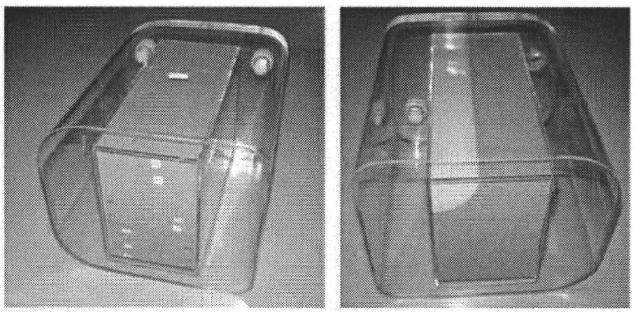

図１：水タンク式不均質肺ファントムの画像。右肺野用（左図）と心臓の模擬腫瘍がある左肺野用（右図）。

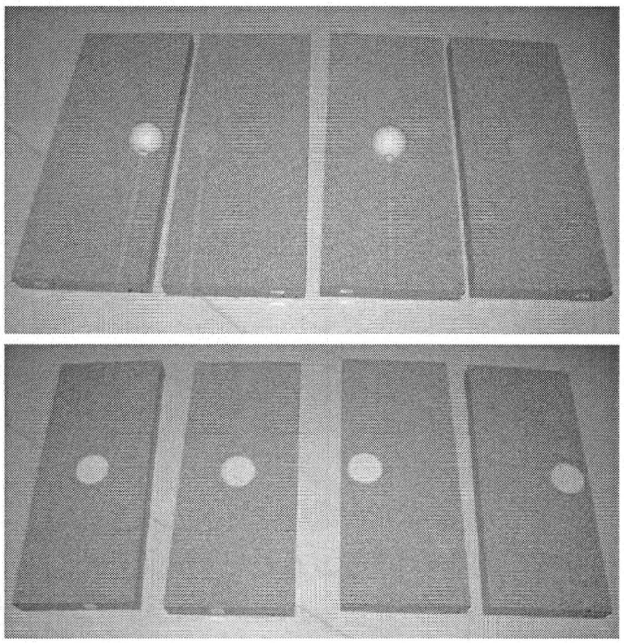

図２：模擬腫瘍を含む肺野コルクの割面画像。上図はPTW製PinPoint線量計用、下図は線量分布測定フィルム用。

水タンク式不均質肺ファントムは、肺野部分がコルク、3cmφの球形をした模擬腫瘍部分がタフウォーター、その他の部分は水で充填された3mm厚のアクリル容器で構成されている。実装するコルクを組み合わせることで、模擬腫瘍の位置を肺野中で動かすことが可能である。模擬腫瘍中心にPTW社製の3D PinPoint電離箱などの微小容積電離箱が設置可能である（図２上図参照）。また、水を抜けば非常に軽量であるため、郵送による多施設の治療計画装置の管理検証ツールとしても十分利用可能である。電位計はUNIDOSを利用する。ISP社製のGAFCROMIC FILMを利用することで、模擬腫瘍の中心を通る割面を含んだ肺野中での３面（アキシャル・サジタル・コロナル）の線量分布測定が可能である（図２下図参照）。

図３は施設訪問調査で利用する使用機器一式である。

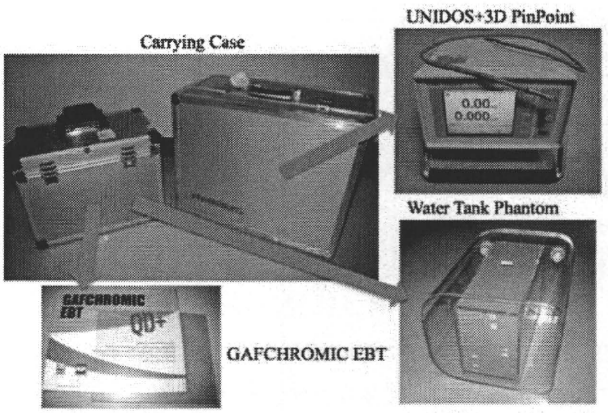

図３：施設訪問調査使用機器一式。

模擬腫瘍を、肺野中心、胸壁近傍の計３つの位置に設置し、治療計画用のCT撮影を各腫瘍位置の場合について実施した。各腫瘍位置に対して、３つの計画（plan id#1-3）を実施した（図４参照）。Plan id#1及び2の照射ガントリー角度及び計画線量は20、315及び260度の３門及び600cGy、plan id#3は貴施設での体幹部定位照射法に則した照射角度及び1200cGyの計画線量で行った。模擬腫瘍より5mmの３次元マージンを付けたものをPTV、MLCマージンはリーフ幅中心点でPTV外接から5mm、線量計算は不均質補正を考慮し、搭載された最上位の線量計算アルゴリズムを利用した。対象となった治療計画装置／線量計算アルゴリズムは、CMS社製XiO／Superposition、Varian社製ECLIPS／AAA、BrainLab社製iPlan／MCであった。腫瘍中心に3D PinPoint電離箱を挿入し、３つの計画のそれぞれに対して、治療計画装置より計算された600cGy及び1200cGyのMU値で照射及び実測した（図３参照）。ISP社製のGAFCROMIC EBTフィルムを利用して、３つの計画のそれぞれに対して、治療計画より計算されたMU値の

200cGy 相当分（既に算出された MU 値を 1/3（plan id#1 及び 2）、1/6（plan id#3））の照射により、腫瘍中心を含む、コロナール面（plan id#1、2 及び 3）・アキシャル面（plan id#3 のみ）の線量分布測定を実施し、線量計算精度検証システムの有用性を評価した。

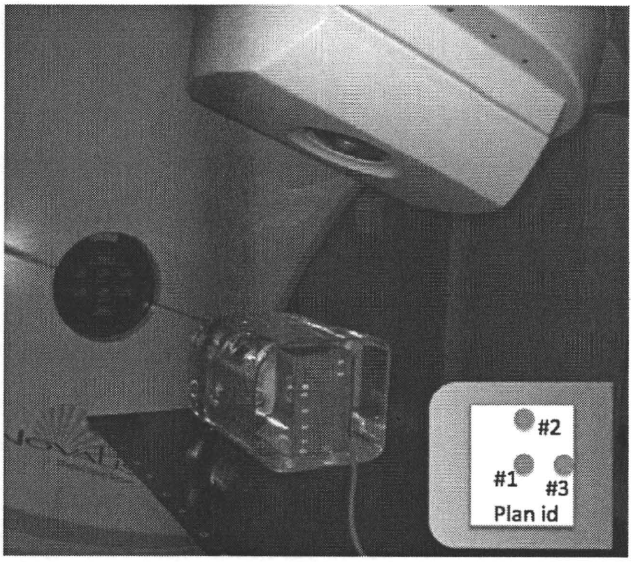

図４：計画されたビームのファントムへの照射風景。

C．研究結果

表１は、各計画に対する、腫瘍中心での線量計算結果と電離箱線量計による実測結果及びそれらの相違結果の例である。線量実測値に対する線量計算値の相違は 1%以下であった。図５は GAFCROMIC EBT フィルムによって得られた線量分布実測結果である。

表１：腫瘍中心での線量計算及び実測結果の例。

Plan ID	Gantry[deg.]	Bed[deg.]	治療計画計算結果			実測線量結果		相違（計算値-実測値）/実測値	
			cGy		MU	cGy		%	
1	20	0	200	600	271	198.6	595.7	-0	-1
	315	0	200		307	198.4		-1	
	260	0	200		313	197.7		-1	
2	20	0	200	600	242	201.6	599.7	+1	0
	315	0	200		254	199.1		0	
	260	0	200		313	199.1		0	
3	180	0	150	1200	198	150.3	1202.3	0	0
	140	0	150		216	152.2		+1	
	90	0	150		217	151.5		+1	
	25	90	150		205	148.6		-1	
	335	310	150		206	149.0		-1	
	325	60	150		209	149.4		-1	
	250	0	150		257	150.8		0	
	200	0	150		201	151.3		+1	

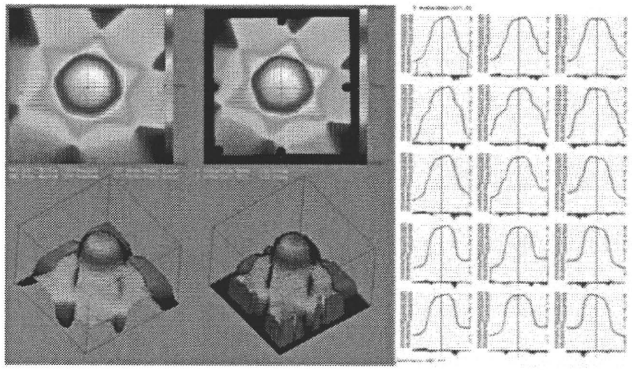

図５：治療計画による線量分布計算結果と GAFCROMIC EBT フィルムによる線量分布実測結果の比較検証の例。

D．考察

水タンク不均質肺ファントムによる、微小電離箱線量計及び現像を必要としない線量測定フィルムを用いた施設訪問調査用の線量計算精度検証システムは、治療計画装置による線量計算精度を検証する上で、有用なシステムであると言える。

腫瘍中心の線量測定は、方向依存性が少ないとされる、放射線に対する微小有感体積を持つ 3D PinPoint 電離箱を利用した。どの方向からも、空間分解能が高い利点を有しているが、基準電離箱とされる Farmer 型（PTW/30013 など）と比較すると、放射線の線質依存における測定値の僅かな相違が、施設訪問調査の事前の線量検証によって観測された。3D PinPoint 電離箱線量計を水タンク式肺ファントムによる治療計画装置の検証に利用するには、今後も十分な測定線量の特性などの検証が必要である。また、GAFCROMIC EBT フィルムを利用した線量分布検証において、現像を必要としないフィルムであることから、現像作業による変動を無視することが出来る、照射の際の扱いが容易などの利点はある。その一方で、現像を必要とする EDR2 フィルムと比較すると、黒化度の安定性などは低く、施設訪問で取得した線量分布プロファイルの結果を観ても、ノイズ成分が観測されている。更に、現在、GAFCROMIC EBT フィルムは生産中止の状況にあり、新たに GAFCROMIC EBT2 フィルムが発売されている。この双方のフ

ィルムは構造上の違い等あるため、今後、GAFCROMIC EBT2 フィルムの利用へ切り替えるためのフィルム検証作業が必須である。今後のフィルム開発に期待するところである。

E．結論

肺の体幹部定位放射線治療における治療計画装置の線量計算精度検証システムを開発し、JCOG0702プロトコール参加の多施設訪問調査によってその有用性を評価した。

今回、製作した水タンク式不均質肺ファントムを用いた線量計算精度検証システムは体幹部定位放射線治療の治療計画による線量計算精度の検証において有用であることを示唆できた。

F．健康危険情報

特記事項なし

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SPECIAL FEATURE

Strategies of radiotherapy for recurrent and metastatic breast cancer

Radiation therapy for brain metastases in breast cancer patients

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Abstract Most randomized comparison trials (RCTs) investigating treatments for brain metastases (BM) have included BM from any origin; as a result, more than half (52.4–77.0%) of the BM in these trials originated from the lungs (mostly non-small-cell lung cancer, NSCLC), with the breasts being the origin in only 6.8–19.0% of cases. In addition, patients with poor systemic status (KPS < 70) were not included in these trials. Hence, before we can apply RCT-based information to the daily clinical treatment of BM from breast cancers, it will be crucial to differentiate the characteristics of BM originating from NSCLC and BM originating from breast cancer. Although stereotactic radiosurgery (SRS) is widely used in Japan, level-1 evidence suggests that the benefit of using SRS in addition to whole-brain radiation therapy (WBRT) has been proven only for patients with a single BM. Treatment with SRS alone, which is widely used in Japan, seems attractive because it could avoid the risk of long-term adverse effects of WBRT. However, level-1 evidence suggests that the omission of WBRT results in a high frequency of brain tumor recurrence (BTR). In an RCT between SRS-alone and SRS + WBRT conducted in Japan, we found that patients who had a single BM and no extracranial metastases had a low risk of developing BTR after initial brain management (low-risk group) compared with those who had 2 or more BM and extracranial metastases (high-risk group). In order to meet the criteria of "low-risk" BTR, patients also should have good systemic status (KPS ≧ 70). Epidemiologic data suggest that the prognosis is twice as likely to be poor in patients with BM from breast cancer (RPA III = KPS < 70) than in patients with BM from NSCLC (40 vs. 20%); in addition, the probability of brain-only metastases in patients with breast cancer is less than half that in patients with NSCLC (20–25 vs. 60–75%). Considering these findings, we should be aware that most patients with BM from breast cancer are not good candidates for SRS alone, and, therefore, the role of WBRT is still important in the era of modern radiation techniques.

Keywords Breast cancer · Brain metastases · Radiation therapy · Stereotactic radiosurgery · Whole-brain radiation therapy

Introduction

Brain metastases (BM) are a common complication for patients with solid cancer; approximately 20% of cancer-sufferers develop BM and patients with breast cancer are not an exception. In a study based on autopsy data, it was reported that BM was found in 193 (18.5%) of 1044 cases of breast cancer [1]. Among patients with BM of any origin, however, the lungs are the primary tumor site, accounting for 40–50% of all cases, whereas the breasts are the origin in only 10–20% of cases [2–5]. In six prospective randomized controlled trials (RCTs) investigating treatment for BM (Table 1), the lungs were the predominant tumor site, accounting for between 52.4 and 77.0% of cases, whereas the breasts accounted for only 6.8–19.0% of cases [6–11]. In addition, small-cell lung cancer (SCLC) was excluded in those RCTs. Therefore, we should keep in mind that most data on the treatment of BM are strongly

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Table 1 Level 1 evidence dealing with the treatment of brain metastases

Author, year	Number of BM	*N*	Primary tumor site (%)			Median survival time (months)		*P*
			Breast	Lung (NSCLC)				
					Treatment arms	Surgery + WBRT	WBRT alone	
Patchell, 1990	Solitary	48	6.3	77.1		9.2	3.5	<0.01
Vecht, 1993	Solitary	63	19.0	52.4		10	6	0.04
Mintz, 1996	Solitary	84	11.9	53.6		5.6	6.3	NS
					Treatment arms	SRS + WBRT	WBRT	
Andrews, 2004	1–3	333	10.2	63.4		5.7	6.5	NS
					Treatment arms	Surgery + WBRT	Surgery alone	
Patchell, 1998	Solitary	95	9.5	60.0		11.0	9.9	0.39
					Treatment arms	SRS + WBRT	SRS alone	
Aoyama, 2006	1–4	132	6.8	66.7		7.5	8.0	0.42

BM brain metastases, *NSCLC* non-small-cell lung cancer, *WBRT* whole-brain radiation therapy, *SRS* stereotactic radiosurgery

affected by the characteristics of patients with primary non-small-cell lung cancer (NSCLC). So far, there has been no RCT dealing exclusively with BM of breast cancer patients. Hence, before we can apply RCT-based information to the daily clinical treatment of BM from breast cancers, it will be crucial to differentiate the characteristics of BM originating from NSCLC and BM originating from breast cancer.

Clinical features

Time interval between diagnosis of primary cancer and the development of BM

Boogerd et al. [12] reported that the interval between diagnosis of primary cancer and the development of BM among patients with breast cancer was ≤12 months in only 11% of patients and as much as 23% of BM developed ≥60 months after the initial diagnosis. A similar trend was found in other retrospective [13, 14] or prospective [15] studies: the median time to the development of BM from the diagnosis of primary cancer was 30–40 months for patients with breast cancer, which is significantly longer than the time interval of 3–4 months [2, 14, 16] observed in cases of NSCLC. A short interval to the development of BM from NSCLC was also seen in a retrospective review of 422 patients with stage IIIA/B NSCLC in the Southwest Oncology Group (SWOG) database who received multimodality treatment. BM developed in 71 of 422 patients; 33 (46.5%) of these patients experienced BM within 6 months after the treatment and only 12 (17%) relapses occurred 12 months and after [16]. As a result, a significant difference in the cumulative incidence of BM was observed, depending on the type of primary cancer. Schouten et al. [15] reported that the 5-year cumulative incidence of BM was as high as 29.7% in SCLC and 12.6% in NSCLC, whereas it was only 5.0% in patients with breast cancer.

Risk factors of developing BM among patients with breast cancer

A number of patient and tumor characteristics, including younger age (premenopausal or <50 years) [17], the presence of lung or liver metastases [17], negative hormone-receptor (HR) status [18], larger tumor size [19, 20], larger number of involved lymph nodes [20, 21], and positivity for human epidermal growth factor receptor 2 (HER2) [19, 22], have been identified as risk factors for developing BM [18, 20, 21, 23–25]. Regarding the relationship between HER2 status and the incidence of BM, patients with HER2-positive breast cancer are at risk of developing BM, with cumulative incidence as high as 30–50% [17, 22, 24, 26, 27]. Duchnowska et al. [22] reported that the median time from treatment of the primary tumor to brain relapse for HER2-positive patients was 15 months, which is much shorter than that for all breast cancer patients [2, 13], and the cumulative 1-year, 3-year, and 5-year risks for those patients were 17, 42, and 55% respectively [22]. This trend of shorter duration until the development of BM in HER2-positive compared with HER2-negative patients was confirmed in another series [28]. In relation to HER2 status and the incidence of BM, it remains a matter of controversy whether trastuzumab, a recombinant humanized monoclonal antibody targeted against the extracellular domain of HER2, actually increases the risk of BM. In a meta-analysis of five RCTs in which the outcomes of adjuvant trastuzumab treatment for HER2-positive early breast cancer were compared, the likelihood of developing BM

was 1.82-fold higher (95% CI: 1.16–2.85) in patients who received trastuzumab treatment [29]. However, none of these comparison studies showed a significant difference in the incidence of BM between patients who received and those who did not receive trastuzumab therapy [27, 28, 30]. In a recent review of the literature, the incidence of CNS metastases in trastuzumab-treated patients was found to be similar to that in patients with HER2-positive disease [24].

The incidence and the pattern of BM in relation to hormone receptor and HER2 status was investigated in further detail by Niwinska et al. [31]. They divided patients into three subtypes: triple-negative (ER/PgR negative, HER2 negative), HER2-positive (any ER, any PgR, HER2 positive), or luminal (ER/PgR+, HER2 negative) patients. Patients classified in the triple-negative subtype experienced BM as the first site of dissemination more frequently (26%) than those in the HER2-positive (6%) or luminal (12%) subtypes.

Number of brain metastases (Table 2)

In their 1996 retrospective study, Nussbaum et al. [2] reported that there seemed to be no significant difference in the number of BM between patients with NSCLC and those with breast cancer; the pattern of BM was single in 50% of NSCLC, 44% of SCLC, and 49% of breast cancer patients with BM. In more recent retrospective studies, the frequencies of single BM among breast cancer patients with BM were around 40% [32–34] (Table 2), which seems to be smaller than the value in the older series reported in the 1990s; however, a similar trend could be seen in patients with BM of NSCLC, as shown in Table 2. In a prospective clinical study by Socinski et al. [35] designed to evaluate the safety of bevacizumab in 115 patients with BM from NSCLC, the number of BM was single in 31 patients (27.0%), 2–4 in 43 patients (37.4%), and 5 or more in 41 patients (35.7%). This trend toward a reduction in the rate of single BM may be partially attributable to advances in the imaging technologies [36].

Prognosis and related factors

The most widely accepted prognostic classification for patients with overt BM has been recursive partition analysis (RPA), which was proposed by Gaspar et al. [37] on the basis of the review of three RTOG studies. In this RPA classification, patients were divided into three prognostic groups based on age, KPS, and extracranial disease status. The best survival (RPA class I), with a median of 7.1 months, was observed in patients who were aged <65 years, whose KPS was ≥70, and whose primary tumor was controlled, with the brain as the only site of metastasis. The worst survival (RPA class III), with a median of 2.3 months, was seen in patients with KPS < 70. The remaining patients (RPA class II) had a median survival of 4.2 months [37]. In this analysis, however, only 12% of patients had BM from breast carcinoma; therefore, it remains uncertain whether the RPA classification can be safely applied to BM from breast cancer. The results of my literature review regarding the distribution and prognosis of patients with BM according to RPA class, the type of primary tumor and the predominant treatment method (whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), or surgery) are summarized in Table 3.

Table 2 Number of brain metastases among patients with breast cancer and other types of cancer

Author	Publication year	Origin	Number of brain metastases		
			N	Single (%)	Multiple (%)
Nussbaum	1996	Breast	121	49	51
Goyal	2005		43	40	60 (2–4 lesions 58%, 5 lesions 2%)
Liu	2006		48	44	56
Viani	2007		174	38	62
Akyurek	2007		49	47	53 (2–3 lesions 39%, 4 or more 14%)
Lee	2008		198	28	72
Nussbaum	1996	Lung (NSCLC)	178	50	50
Socinski	2009		115	27	73 (2–4 lesions 37%, 5 or more 36%)
Mehta	2003	Any (Breast 18.7%)	401	20	79 (2–3 lesions 34%, 4 or more 45%)
Andrews	2004	Any (Breast 9.5%)	333	56	44 (2 lesions 26%, 3 lesions 18%)
Aoyama	2006	Any (Breast 6.8%)	132	48	52
Fraizer	2009	Any (Breast 14%)	237	42	58 (2–3 lesions 36%, 4 or more 22%)