Table 2. Univariate analysis of local tumor control and cause-specific survival

| Factor (*n*) | Local tumor control *p* value | Cause-specific survival *p* value |
|---|---|---|
| Age | | |
| <65 yrs (10)/≥65 yrs (21) | NS | 0.058 |
| Sex | | |
| Male (12)/female (19) | NS | NS |
| Primary site | | |
| NC (16)/PS (7)/others (8) | NS | NS |
| Stage | | |
| I (27)/II (4) | NS | NS |
| Dose per fraction | | |
| 1.5–2.5 Gy (14)/3–13.8 Gy (17) | 0.048 | 0.045 |
| Total dose | | |
| ≤50 Gy (16)/>50 Gy (15) | NS | NS |
| BED | | |
| ≤118 Gy (17)/>118 Gy (14) | (0.037) | (0.033) |
| Overall treatment time | | |
| <40 days (17)/≥40 days (14) | NS | NS |
| Operation | | |
| no (21)/yes (10) | NS | NS |
| Chemotherapy | | |
| no (19)/yes (12) | NS | NS |
| Immunotherapy | | |
| no (20)/yes (11) | NS | NS |
| Clinical response | | |
| CR (9)/PR+NC (22) | NS | NS |

*Abbreviations:* CR = complete response; PR = partial response; NC = no change; NS = not significant ($p > 0.1$).

Biologically equivalent dose (BED) = $nd\left(1 + \frac{d}{\alpha/\beta}\right)$ in Gy, where $n$ is the fractionation number and $d$ is daily dose. We used the $\alpha/\beta$ ratio of 2.5 Gy for malignant melanomas advocated by Overgaard *et al.*, who expressed the BED as the extrapolated total dose. The BED was used as a reference factor in the present study because we could not determine whether the $\alpha/\beta$ ratio of 2.5 Gy could be applied correctly to mucosal melanoma of the head and neck.

## RESULTS

Of the 31 tumors, 9 (29%) disappeared completely after treatment (complete response) and 18 (58%) decreased in size by ≥50% after treatment (partial response). Thirteen patients (41.9%) suffered local recurrences. Cervical lymph node metastases outside the treatment field and distant metastases developed in 5 patients (16.1%) and 11 patients (35.5%), respectively. Figure 1 shows the local tumor control and distant metastasis-free survival of all patients. Most incidences of local recurrences and distant metastases developed within 2 years after the initial treatment. Overall cause-specific survival rates at 1- and 3-year were 73% and 33%, respectively (Fig. 2).

The results of univariate analysis are shown in Table 2. The dose per fraction was significantly related to prognosis, with the HF-RT group showing better prognoses for both local tumor control (Fig. 3a) and cause-specific survival (Fig. 3b). A BED conversion of more than 118 Gy was also significantly related to better prognoses for both local tumor

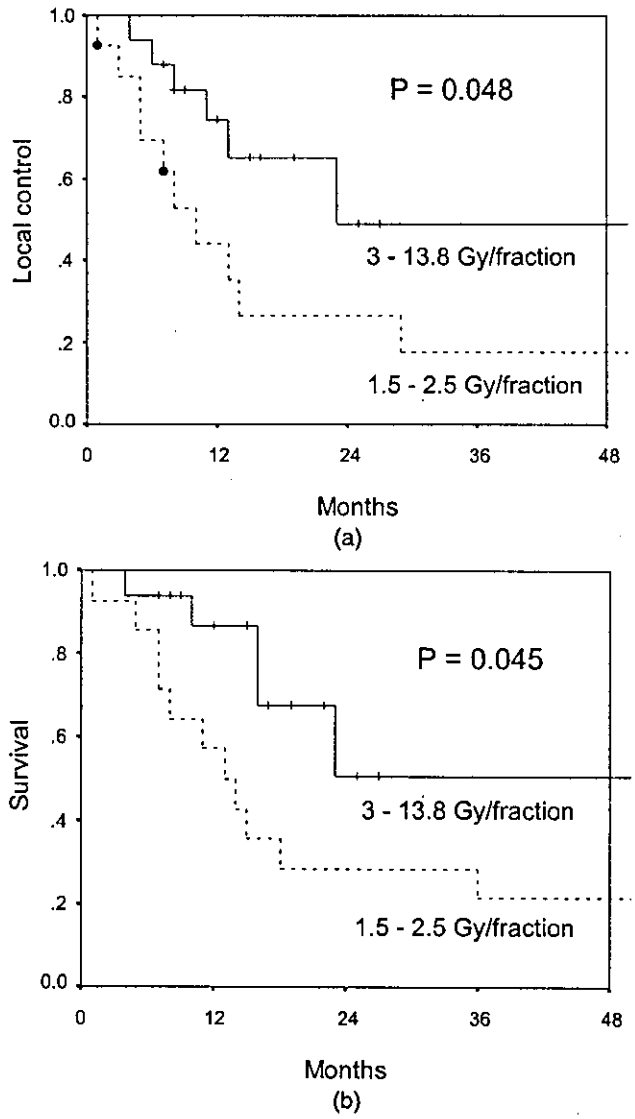


Fig. 3. (a) Local tumor control and (b) cause-specific survival for the group receiving the high-dose and low-dose per fractionated radiotherapy.

control (Fig. 4a) and cause-specific survival (Fig. 4b). The dose per fraction was strongly correlated with the BED: 76% (13/17) of patients in the HF-RT group received radiotherapy at a dose of more than 118.8 Gy in the BED conversion, whereas only 7% (1/13) of those in the LF-RT group received radiotherapy at such high doses (chi-square test, $p = 0.001$). Age showed borderline significance as a prognostic factor for cause-specific survival (Fig. 5, $p = 0.058$).

We also examined possible prognostic factors for local tumor control and cause-specific survival with Cox's regression analysis. None of these factors was significant for local tumor control. Age was selected as the only significant prognostic factor for cause-specific survival (better in younger patients, $p = 0.046$).

Acute mucositis occurred in 5 patients (4 in the LF-RT group and 1 in the HF-RT group) requiring radiotherapy to

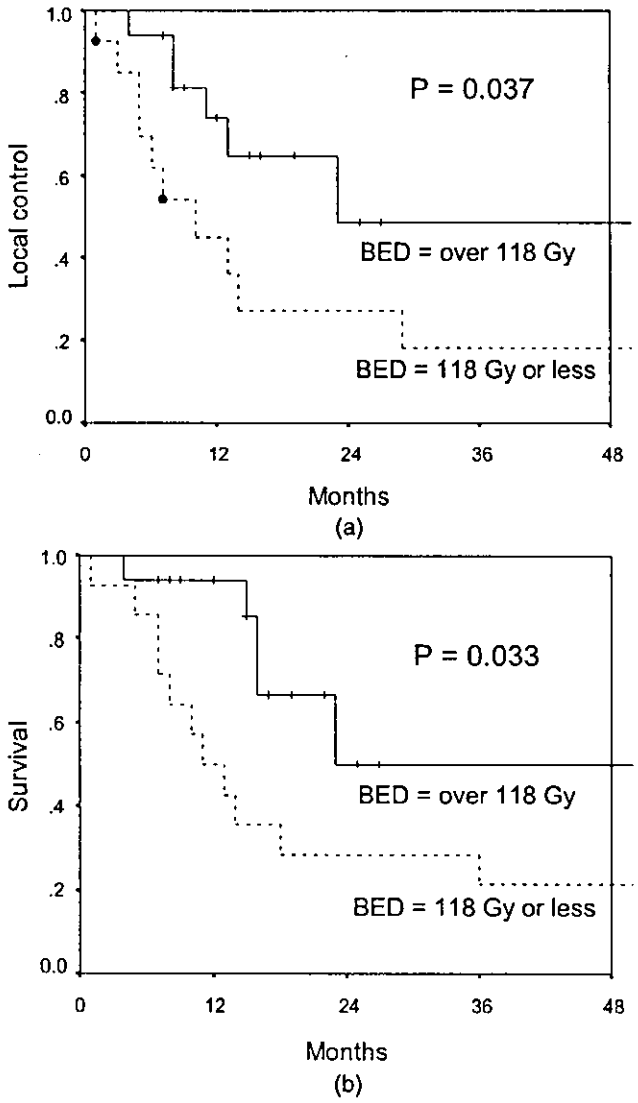


Fig. 4. The effect of the biologically equivalent dose (BED [$\alpha/\beta$ = 2.5 Gy]) on (a) local tumor control and (b) cause-specific survival.

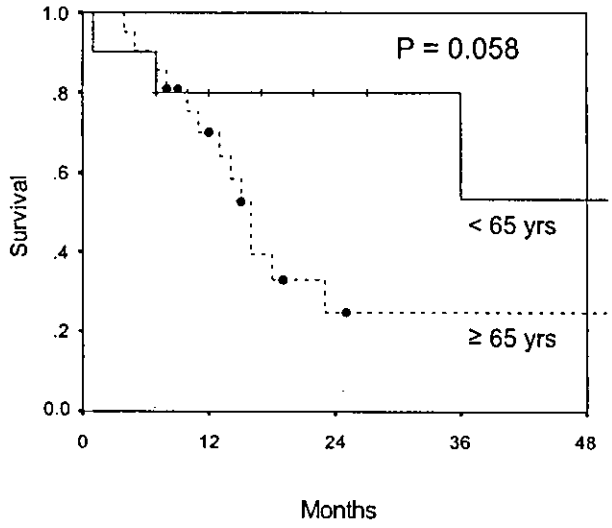


Fig. 5. The effect of age on cause-specific survival.

be paused for more than a week, but all of these patients completed the course of treatment. Fatal late complications occurred in 2 patients (6.5%). One patient with nasal melanoma treated with a total dose of 49.6 Gy in 13 fractions had severe mucosal ulceration in the soft palate. The other patient with nasal melanoma treated with a total dose of 36 Gy in 6 fractions had fatal nasal bleeding. None of the patients showed radiation-induced brain necrosis or myelopathy.

## DISCUSSION

The prognosis for patients with mucosal melanoma of the head and neck is poor. A review of more than 1,000 patients with this disease revealed that 5- and 10-year survival rates were 17% and 5%, respectively (8). Local recurrence is the initial cause of failure for localized mucosal melanoma of the head and neck, whereas distant metastases also develop frequently (7, 8). Some authors suggested that aggressive local treatment should be initiated at presentation of localized melanomas because the achievement of local tumor control provides the possibility of an increase in survival rate (7, 17).

There have been few reports of clinical analysis of radiotherapy for localized mucosal melanoma of the head and neck. A review of four previous reports by Trotti *et al.* (14) showed 3-year local control rates of 36%–61%. In the present study, the 3-year local tumor control and cause-specific survival rates were only 30% and 33%, respectively. Unfortunately, many patients suffered local recurrences and died within 2 years.

A better prognosis was significantly related to HF-RT in both local tumor control and survival, as compared with LF-RT. Harwood *et al.* (13) analyzed local control vs. the fraction size of primary irradiation and reported that significantly more patients treated with a dose per fraction of ≥4 Gy achieved complete regression compared with those receiving a dose per fraction of ≤3.99 Gy. Shibuya *et al.* (15) reported that high-dose radiotherapy at a dose of 70–80 Gy delivered in 7–8 fractions with an intraoral electron beam was effective for local control of mucosal melanoma of the upper jaw. Trotti *et al.* (14) concluded that definitive radiotherapy was effective and they recommended the use of HF-RT based on a review of four previous reports, although they did not refer to the survival benefit of HF-RT. The results of the present study also supported the clinical conclusions of these previous reports.

An optimal total dose of radiotherapy for localized mucosal melanoma of the head and neck has not been determined. Overgaard *et al.* (17) reported that the BED, expressed as the extrapolated total dose in their report, for the 50% complete response line of malignant melanoma was 125 Gy. Based on these observations, Trotti *et al.* (14) recommended a total dose of 36 Gy delivered in 6 fractions

(122.4 Gy in the BED conversion) for mucosal melanoma of the head and neck. The total dose of radiotherapy applied with an intraoral electron beam reported by Shibuya *et al.* (15) was 350–400 Gy in the BED conversion, but the utility of the electron cone may be limited to specific anatomic sites. The BED of more than 118 Gy in the present study also showed excellent results with regard to local tumor control and survival, although there are doubts regarding whether the $\alpha/\beta$ ratio of 2.5 Gy can be applied correctly to mucosal melanoma of the head and neck. Most patients in the HF-RT group received a BED of more than 118 Gy, similar to the dose proposed by Trotti, and these two factors were strongly correlated. We assume that a BED of at least 118 Gy (i.e., approximately 40 Gy in 8 fractions, 44 Gy in 11 fractions, and 54 Gy in 18 fractions) may be effective when deciding the total dose of HF-RT.

Some authors suggested that postoperative radiotherapy appeared useful for local tumor control for mucosal melanoma of the head and neck (14, 18). However, in the present study radiotherapy did not have a significant positive effect on local control of gross residual lesions after surgery. This may have been because 90% (9/10) of the patients in the postoperative radiotherapy group received LF-RT. In fact, median period of local tumor control in the postoperative radiotherapy group (13 months) seemed to be longer than that in the LF-RT alone group (7 months). Therefore, postoperative radiotherapy itself might be effective by debulking tumor volume. Stevens *et al.* (19) reported the efficacy of postoperative HF-RT for locally advanced melanoma. Use of the combination of surgery and postoperative HF-RT may produce a better outcome with regard to local tumor control and sequential survival benefit. However, the outcome of postoperative radiotherapy for mucosal melanoma of the head and neck has not been reported with regard to comparison of the differences in dose per fraction.

The development of distant metastases after treatment is a serious problem associated with this disease. Pooled data from 12 series reviewed by Mandolis *et al.* (8) showed the average distant metastatic rate after treatment to be 51.5%. In the present study, the 3-year distant metastasis-free survival rate was 56% and most distant metastases were observed within 2 years after the initial treatment. Many studies using different combinations of chemotherapeutic and immunotherapeutic agents to overcome this disease have been performed, but chemotherapy and immunotherapy were utilized in a noncontrolled fashion as adjuvant therapy, with consistently disappointing results (8). Our analysis also revealed the negative outcome of local tumor control and survival benefit. To date, the efficacy of chemotherapy and immunotherapy for mucosal melanoma for the head and neck has been controversial.

In the present study, multivariate analysis showed that better cause-specific survival was achieved in younger patients (<65 years). Unfortunately, the study population was very small and we cannot explain why younger patients had a better prognosis on multivariate analysis. However, Nandapalan *et al.* (8) also reported that young patients with mucosal melanomas of the head and neck tended to have a favorable prognosis. They suggested that younger patients should receive aggressive local treatment if feasible, as this offered the best chance of achieving a complete cure.

In the present study, fatal late complications occurred in 2 cases in the HF-RT group. The total radiation dose to the target must be limited, especially in the HF-RT group, to avoid affecting adjacent critical structures, and minimize the possibility of late adverse effects in normal tissue. It is important to plan radiotherapy for mucosal melanoma of the head and neck carefully with special irradiation techniques, such as three-dimensional conformal radiotherapy or intensity modulated radiotherapy to increase the tumor dose without exceeding the radiation tolerance of the surrounding structures (20). Recently, a preliminary study with carbon ion therapy for mucosal melanoma of the head and neck demonstrated excellent local control (local control with a median 20 months in 19 of 20 patients) at the National Institute of Radiologic Sciences in Japan (21). In future, such treatment approaches may provide new strategies to overcome this fatal disease.

In conclusion, we showed that radiotherapy with a dose per fraction of ≥3 Gy achieved good local tumor control and good subsequent survival especially in younger patients with mucosal melanoma of the head and neck. The treatment still failed in half of all patients, however, and further investigations are required to establish a better clinical outcome in the treatment of this disease.

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**Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma: Clinical outcomes in 273 cases of a Japanese multi-institutional study.** *H. Onishi, Y. Nagata, H. Shirato, K. Gomi, K. Karasawa, T. Arimoto, K. Hayakawa, Y. Takai, T. Kimura, A. Takeda; Yamanashi University, Faculty of Medicine, Yamanashi, Japan; Kyoto University, Faculty of Medicine, Kyoto, Japan; Hokkaido University, Faculty of Medicine, Sapporo, Japan; Cancer Institute Hospital, Tokyo, Japan; Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; Kitami Red-cross General Hospital, Kitami, Japan; Kitasato University, Kanagawa, Japan; Tohoku University, Sendai, Japan; Hiroshima University, Hiroshima, Japan; Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan*

**Background:** Stereotactic hypofractionated irradiation (STI) has been actively performed for a radical treatment of stage I non-small cell lung cancer (NSCLC) in Japan. We sought to retrospectively evaluate Japanese multi-institutional results. **Methods:** From April 1993 to April 2003, 273 patients (age range 35–92, median 76 years) who had stage I (175 T1N0M0 and 98 T2N0M0) primary NSCLC (119 squamous cell, 125 adeno, and 29 others) were treated with hypofractionated high-dose STI in 14 institutions. Of the 273 patients, 169 (61.9%) were medically inoperable due to mainly chronic pulmonary disease or high-age. Tumor size ranged from 7 to 58 mm with a median of 28 mm. The stereotactic three-dimensional treatment was performed using non-coplanar dynamic arcs or multiple static ports. A total dose of 18–75 Gy at the isocenter of tumors in 1–22 fractions was administered. The calculated biologic effective dose (BED, $\alpha/\beta=10$) ranged from 57 Gy to 180 Gy with a median of 105. **Results:** All patients completed the treatment with no complaints. During the follow up of 7–127 (median=24) months, pulmonary complications greater than NCI-CTC criteria grade 2 were noted in only 6 (2.4%) patients. Of 269 patients who were evaluated with CT, we observed CR and PR in 71 (26.4%) and 159 (59.1%) patients, respectively. The local progression occurred in 34 (12.5%) of total patients, and a lower local recurrence rate was observed (8.0% vs. 26.4%, $P<0.05$) when BED was $\geq$100 Gy vs. <100 Gy. The intercurrent death was observed in 43 (15.8%), mostly in inoperable patients. The 3-year overall survival rate of medically operable patients was 95.2% vs. 69.4% ($P<0.05$) when BED was $\geq$ 100 Gy vs. < 100 Gy. **Conclusions:** Hypofractionated high-dose STI is a feasible and beneficial method for the curative treatment of patients with stage I NSCLC. Local control and survival rates were better for BED $\geq$100 Gy than for BED <100 Gy for all treatment methods and schedules. Survival rate for STI in selected patients (medically operable and BED $\geq$100 Gy) were excellent, potentially equal to those of surgery.

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# Ten-year Disease-free Survival of a Small Cell Lung Cancer Patient with Brain Metastasis Treated with Chemoradiotherapy

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**Abstract.** *We report the first case of 10-year disease-free survival in a patient with small cell lung cancer (SCLC) with brain metastasis. A 63-year-old man was found to have SCLC with brain metastasis and underwent chemoradiotherapy. Radiation therapy was delivered to the brain, lungs, mediastinum and supraclavicular fossa. Chemotherapy regimen mainly consisted of etoposide-plus-cisplatin. The patient has remained alive for more than 10 years after the diagnosis of SCLC with brain metastasis with no relapses.*

Chemoradiotherapy has recently improved the treatment results of limited-stage small cell lung cancer (LD-SCLC). Turrisi *et al.* reported that the 5-year overall survival rate of patients with LD-SCLC was 26% (1). On the other hand, patients with extensive-disease small cell lung cancer (ED-SCLC) can not survive for a long time. The most promising treatment, iriontecan-plus-cisplatin (IP), has increased the survival time of patients with ED-SCLC more than treatment with etoposide-plus-cisplatin (EP). However, the median survival time of patients with ED-SCLC treated with IP was 12.8 months and their 2-year survival rate was 19.5%; these results are much inferior to the results of patients with LD-SCLC (2). The prognosis of cases of SCLC with only brain metastasis was considered to be better than that of other ED-SCLC cases. Ruby *et al.* reported that the median survival time of patients with SCLC with only brain metastasis was 14 months (3). However, only a few cases have been reported of patients with SCLC with brain metastasis surviving more than 5 years (3, 4). No cases have been reported of patients with LD-SCLC with brain metastases achieving a 10-year survival.

We report the first case of 10-year disease-free survival of a patient with SCLC with brain metastasis treated by chemoradiotherapy.

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*Key Words:* Small cell lung cancer, brain metastasis, radiation therapy, chemotherapy.

## Case Report

A 63-year-old man had experienced cough and bloody sputum since July 1993. In September 1993, a mass was palpable on the left side of his neck. His symptoms gradually worsened. He was admitted to the regional hospital and an abnormal shadow in the left lung was found on the chest radiograph. He was introduced to the Tokyo Metropolitan Komagome Hospital, Japan, for further detailed examinations; small cell lung cancer (SCLC) was diagnosed from a biopsy sample obtained by broncho-fiberscopy. Computed tomography of the chest and abdomen and magnetic resonance imaging of the brain were performed; a large tumor was found in the left lung and a small enhanced lesion, indicative of metastasis, was found in his pons (Figures 1 and 2). Thus, the clinical stages were extensive disease (ED) and stage IV (cT2N3M1) according to the UICC-TNM classification. At the time of SCLC diagnosis, the patient's levels of tumor markers for squamous cell carcinoma related antigen (SCC) and serum carcinoembryonic antigen (CEA) were within the normal ranges. However, the level of neuron-specific enolase (NSE) was elevated to 11.8. The patient underwent external irradiation of the entire brain from December 27, 1993 to January 31, 1994, receiving a total dose of 46 Gy. Chemotherapy using cisplatin and etoposide was administered in two cycles between December 12, 1993 and Feburuary 12, 1994. Chest radiographs demonstrated that

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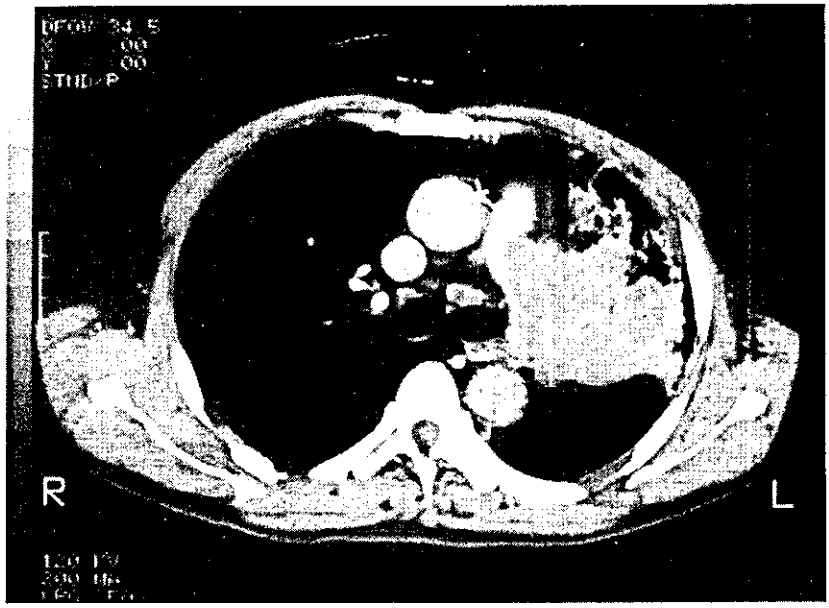


Figure 1. *Computed tomography results of the chest before treatment (mediastinum window). A huge mass was found in the left lung and a small nodule was found in the mediastinum.*

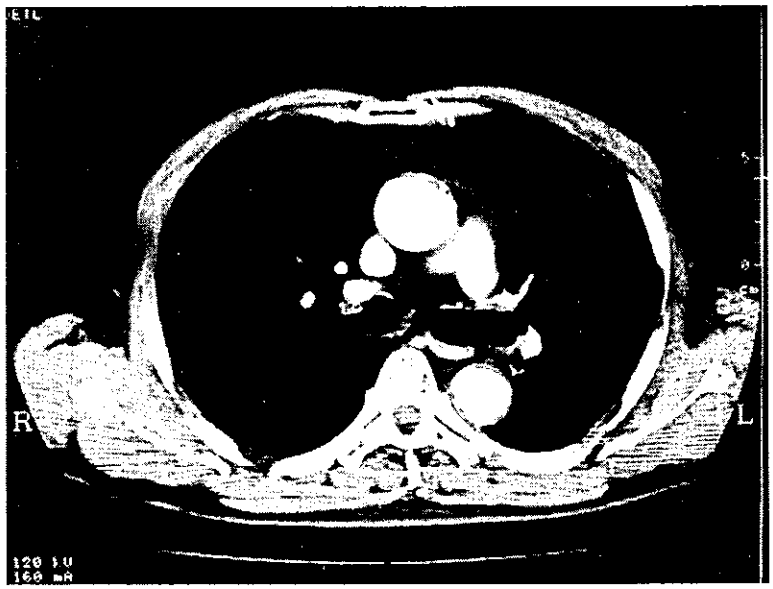


Figure 2. *Computed tomography results of the chest after treatment (mediastinum window). The huge mass had nearly disappeared after chemoradiotherapy.*

the tumor in the left lung had shrunk and decreased in size more than 50%. External irradiation of the lung tumor, mediastinum and supraclavicular fossa was administered from March 15, 1994 to April 22, 1994 (a total dose of 56 Gy, with the cord off after 40 Gy) and 14 Gy of boost irradiation was delivered to the pons lesion (field size, 4 x 5 cm). Concurrent chemotherapy was performed using etoposide and PSK (a protein bound polysaccharide K) as an immunopotentiating biological response modifier. After this treatment, the tumor in the left lung had almost disappeared (Figure 3) and the tumor in the pons completely disappeared (Figure 4). The tumor marker of NSE decreased to 3.8, within the normal range. More than 10 years after the diagnosis of small cell lung cancer with brain metastasis has been made, the patient remained alive without relapse of the disease.

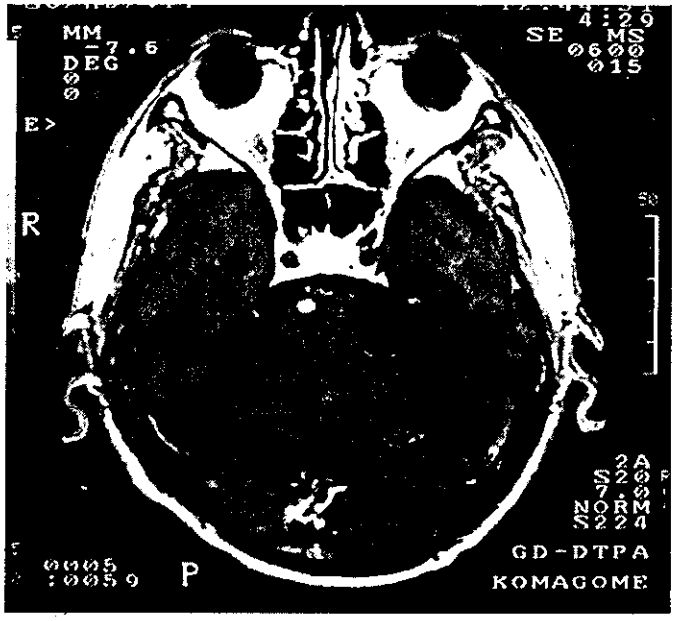


Figure 3. *Computed tomography results of the chest after treatment (mediastinum window). The huge mass had nearly disappeared after chemoradiotherapy.*

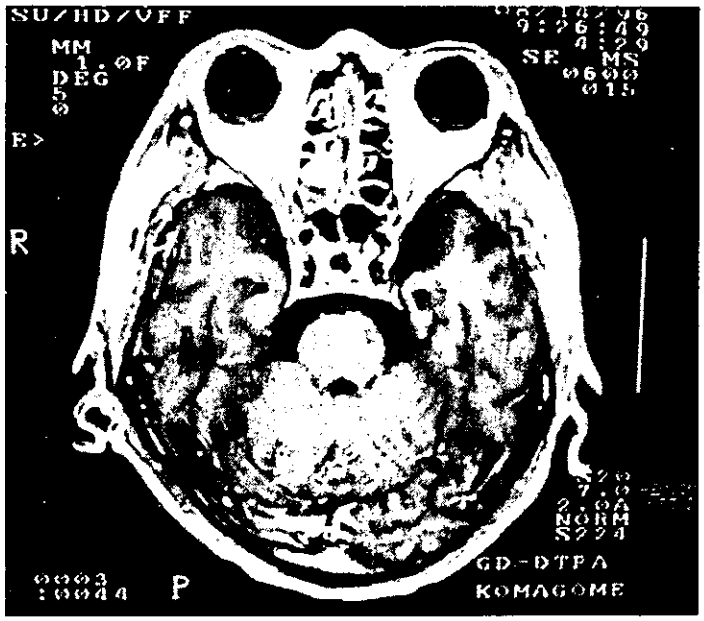


Figure 4. *Enhanced MRI results of the brain before treatment. A small enhanced lesion was found in the pons.*

## Discussion

Small cell lung cancer (SCLC) was reported to comprise about 20% of all lung cancers (5). Of these, about 10% had brain metastases at the time of SCLC diagnosis (6). The prognosis for cases of SCLC with only brain metastases was considered to be superior to those of other ED-SCLC cases. Noda *et al.* reported that the best treatment outcome of ED-SCLC resulted in a median survival time of 12.8 months. The treatment regimen of this study was irinotecan-plus-cisplatin (IP), which meant using a new drug (irinotecan) produced in Japan (2). On the other hand, the median survival time in cases of SCLC with only brain metastasis was reported to be 14.0 months, although these patients were treated with a regimen consisting mainly of cisplatin, etoposide and

cyclophosphamide, which meant it did not include any new drugs (3). Noda *et al.* reported that treatment with etoposide-plus-cisplatin (EP) achieved 9.4 months of median survival in patients with ED-SCLC (2). These findings suggest that treatment of cases of SCLC with only brain metastasis has a relatively better prognosis than treatment of other ED-SCLC cases.

The patient in the current case underwent chemo-radiotherapy to treat SCLC with brain metastasis. The chemoradiotherapy regimen was EP because IP was not recognized as the standard regimen for the treatment of ED-SCLC at the time of his diagnosis. The reason for his long survival is obscure. However, Furuta *et al.* pointed out that some types of SCLC progress slowly and suggested that these should be distinguished from the common type of SCLC (7). SCLC with only brain metastasis might have different biological features from other kinds of ED-SCLC. Moreover, in most SCLC with only brain metastasis, the radiation fields are able to cover all detected tumors. Thus, these patients may be good candidates for appropriate brain and thoracic irradiation combined with chemotherapy if their medical condition and performance status permit aggressive treatment.

In any event, this still appears to be the first demonstration of 10-year disease-free survival of SCLC with brain metastasis after successful treatment.

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# 小型肺癌の治療：
# Ⅰ期非小細胞肺癌の放射線治療

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特集



# 小型肺癌の治療：Ⅰ期非小細胞肺癌の放射線治療

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要　旨

Ⅰ期非小細胞肺癌の放射線治療成績を文献的に検討し，予後因子や再発形式，投与線量，照射野，有害事象などについて考察した。従来の外部照射による治療成績は満足すべきものではなく，治療成績改善に向けた新たな取り組みを述べる。

Key words：Ⅰ期，非小細胞肺癌，手術不能，放射線治療，レビュー/Stage I, non-small cell lung cancer, medically inoperable, radiotherapy, review

## 1 はじめに

Ⅰ期非小細胞肺癌に対して，通常は外科治療が第一選択となる。Mountainによる報告では外科治療におけるIA期の治療成績について，臨床病期による5年生存率は61%であり，切除後の病理病期では67%であった[1]。同様にIB期について，臨床病期による5年生存率は38%であり，病理病期では57%であった。多くの報告で，Ⅰ期非小細胞肺癌の外科治療による5年生存率は50～65%である。

一方，放射線治療は高齢や全身状態不良，肺疾患などの理由により手術不能である症例に対して行われることが多い。したがって，その治療成績はほとんどが遡及的研究によるものであり，報告される症例数も少ない。そして，他病死の頻度が比較的高いことが特徴である。対象を腫瘍サイズが3～4 cm以下といった小さなものに限った報告は少なく，今回はⅠ期の症例全体を対象として文献的考察を行った。

## 2 Ⅰ期非小細胞肺癌に対する放射線治療

### 1) 治療成績

Ⅰ期非小細胞肺癌に対する最近の放射線治療成績を表1に示す。いずれも遡及的研究で，総線量の中央値は60 Gy前後であ

Radiotherapy for Stage I Non-small Cell Lung Cancer
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表 1　早期（I期）非小細胞肺癌に対する放射線治療成績

| 著者 | 症例数 | 年齢(中央値) | IA期(%) | IB期(%) | その他(%) | SCC(%) | 他病死(%) | 全生存率(%) 3年 | 全生存率(%) 5年 | 原病生存率(%) 3年 | 原病生存率(%) 5年 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cheung[2] | 102 | 72 | 33 | 57 | 10 | | 25 | 35 | 16 | 44 | 27 |
| Dosorets[3] | 152 | 74 | 29 | 41 | 27 | | 11 | | 10 | | |
| Graham[4] | 103 | 67 | 31 | 59 | 10 | 48 | 28 | | 13 | | |
| Haffty[5] | 43 | 64 | 28 | 72 | | 53 | | 36 | 21 | | |
| Hayakawa[6] | 36 | | 19 | 81 | | 53 | 22 | 42 | 23 | 56 | 39 |
| Kaskowiz[7] | 53 | 73 | 38 | 62 | | 60 | 27 | 19 | 6 | 33 | 13 |
| Krol[8] | 108 | 74 | 47 | 53 | | | 34 | 31 | 15 | 42 | 31 |
| Morita[9] | 149 | 75 | 40 | 60 | | 50 | | 34 | 22 | | |
| Noordijk[10] | 50 | 74 | 50 | 50 | | | 40 | 33 | 17 | | |
| Sandler[11] | 77 | 72 | 32 | 68 | | 57 | 16 | 17 | 14 | 22 | 17 |
| Sibley[12] | 141 | 70 | 54 | 46 | | 52 | 43 | 24 | 13 | | |
| Talton[13] | 77 | 65 | 3 | 75 | 22 | 84 | | 21 | 17 | | |
| Zhang[14] | 44 | 57 | 14 | 64 | 22 | 64 | 20 | 55 | 32 | | |

SCC：squamous cell carcinoma

[文献15) Sibley GS. Radiotherapy for Patients with Medically Inoperable Stage I Nonsmall Cell Lung Carcinoma. Smaller Volumes and Higher Doses-A Review. Cancer 1998；82：433-8. より一部改変]

る[2)~14)]。その報告の多くが，年齢の中央値が70歳以上の症例を対象にしており，またIA期よりもIB期の比率が高い。さらにいくつかの報告にはI期以外の症例も含まれている。これらの症例群は，他病死の頻度が11～43%と比較的高いが，多くは肺癌が進行しそのために死亡する。大雑把に言って，I期の5年全生存率はおよそ15～20%である。

手術成績は病理病期による報告が多いのに対し，放射線治療成績は臨床病期を用いることが多いため，治療成績を比較検討する際には注意を要する。Narukeらの報告では，臨床病期T1N0の24%，T2N0の32%が病理組織学的にはより進行病期であった[16)]。Martiniらは臨床病期がI期であった216例のうち37%が，病理組織学的にはより進行病期であったと報告している[17)]。また，Lung Cancer Study Group（LCSG）が行った葉切除と部分切除の比較試験でGinsbergらは，臨床病期T1N0のうち25%に術後のupstagingが認められたと報告している[18)]。

### 2）予後因子

多くの研究で，腫瘍サイズが有意な予後因子であると報告している（表2）。日本の10施設からの症例をまとめたMoritaらの報告では，腫瘍径4 cm未満の5年全生存率が25%であったのに対し，4 cm以上では17%であったとしている（p=0.048）[9)]。また，Krolらは腫瘍径4 cm未満の3年原病生存率が40%であったのに対し，4 cm以上では13%であったと報告している（p=0.0005）[8)]。T1とT2の比較では，Noordijkらが5年生存率でT1が26%，T2が15%であったとし[10)]，Grahamらも5年生存率でT1が29%，T2が4%であった（p=0.01）と報告している[4)]。また，Dosoretzらの報告では2年原病生存率がT1で55%，T2で

20%であった[3]。一方で，腫瘍サイズは有意な因子ではなかったとする報告もみられる[5)12)13)]。

病理組織学的検討では扁平上皮癌が有意な予後因子とする報告がいくつかみられるが，これは遠隔転移の頻度が少ないことがその主な理由と考えられる。SibleyらはI期扁平上皮癌の5年原病生存率が39%に対し，その他の組織型では25%であったと報告している（p=0.008）[12]。

また，年齢（70歳未満）はKaskowitzら[7]およびSibleyら[12]の報告では有意な予後因子とされている。

### 3) 再発形式

放射線治療後の再発形式について表3に示す。画像上，照射後の肺の変化と局所再発とが判別困難のことが多い。また，報告によって再発の基準や評価の方法，その時期が異なるため注意を要する。放射線治療後に局所再発を来す頻度はおよそ30～80%と，遠隔転移が起こる頻度（約10～40%）より高い。

一方，外科治療後の局所再発率は低く，LCSGの行った臨床試験の報告では縮小手術群の局所再発率が18%，葉切除群が6.5%であった[18]。また，Harpoleらの解析でも外科治療後のI期非小細胞肺癌の局所再発率は11%と良好である[19]。したがって，放射線治療と外科治療との成績の差は，局所制御率の違いによるところが大きいと考えられる。

### 4) 線 量

投与線量と局所制御率および生存率との関係を検討する。Kaskowitzらは65 Gy未満では局所再発率が50%であったのに対し，65 Gy以上では25%であったと報告している[7]。同様にZhangらの報告では，55～61

表2 I期非小細胞肺癌に対する腫瘍サイズからみた放射線治療成績（括弧の中は年数）

| 著者 | 全生存率(%) | | 原病生存率(%) | |
|---|---|---|---|---|
| | T1 | T2 | T1 | T2 |
| Dosoretz[3] | | | 55(2) | 20(2) |
| Graham[4] | 29(5) | 4(5) | | |
| Krol[8] | 35*(3) | 11**(2) | 40*(3) | 13**(3) |
| Morita[9] | 25*(5) | 17**(5) | | |
| Noordijk[10] | 26(5) | 15(5) | | |
| Sibley[12] | | | 29(5) | 30(5) |

*：腫瘍径≤4 cm
**：腫瘍径＞4 cm
[文献15) Sibley GS. Radiotherapy for Patients with Medically Inoperable Stage I Nonsmall Cell Lung Carcinoma. Smaller Volumes and Higher Doses-A Review. Cancer 1998；82：433-8. より一部改変]

表3 I期非小細胞肺癌に対する放射線治療後の再発形式

| 著者 | | 局所再発（局所再発のみ）(%) | 遠隔転移（遠隔転移のみ）(%) |
|---|---|---|---|
| Dosoretz[3] | T1 | 30 (28) | 9 (6) |
| | T2 | 80 (77) | 40 (33) |
| Haffty[5] | | 39 | |
| Kaskowitz[7] | | 49 | |
| Morita[9] | | 44 | (12) |
| Noordijk[10] | | 70 | |
| Sibley[12] | | 27 (23) | 28 (21) |

Gyでの局所再発率が36%であったのに対し，69～70 Gyでは18%であった[14]。Dosoretzらの報告でも，70 Gy未満での局所再発率が50%であったのに対し，70 Gy以上では33%であった[3]。そして線量を増加させることによって，有意な無病生存率の改善を示した（p=0.0143）。Grahamらは多変量解析によって時間線量分割（TDF）因子が有意な予後因子であることを示した（p=0.002）[4]。また，Sibleyらも多変量解析によって，より高い線量が局所制御率を改善させる因子であることを示した（p=0.07）[12]。これらの報告をまとめると，従来の60～65 Gyの照射に比べて，65～70 Gy以上のより高い線量を照射することによって，局所制御率および無病生存率が改善すると考えられる。またいずれの報告でも，線量増加に伴う有害事象の増加はないとされている。

### 5）照射野

I期非小細胞肺癌に対する放射線治療の照射野に関して，顕微鏡的転移に対する領域リンパ節（縦隔および肺門）への予防的な照射野を含める必要性について検討する。Odaらは，CTで領域リンパ節転移を認めない末梢のT1腫瘍に対してリンパ節郭清術を行い，顕微鏡的領域リンパ節転移の頻度を報告しているが，それによると扁平上皮癌では15%に，腺癌では25%に顕微鏡的転移が認められている[20]。また，手術後の病理組織学的検討によるupstagingは前述したように24～37%である[16)~18)]。

一方で，Krolらは領域リンパ節への予防的照射は行わなかったが，領域リンパ節のみへの再発率は3%であったとし[8]，Sibleyらも同様に7%であったと報告している[12]。また，Hayakawaらの報告では，予防照射を行わなかった26症例中，領域リンパ節のみへの再発は1症例（4%）であった[6]。しかし，Moritaらは領域リンパ節への予防的照射を行った症例で，完全奏効率および5年生存率が改善したと報告している[9]。完全奏効率は予防照射ありが47%，なしが31%（p=0.019），5年生存率は予防照射ありが31.3%，なしが14.9%であった（p=0.022）。

このように，I期非小細胞肺癌に対する放射線治療の照射野をどうするべきか，結論づけることは現時点で困難である。しかしSibleyは，放射線治療の対象となる症例は合併症などによる手術不能例が多く，他病死の頻度が比較的高いこと，また広範囲の照射による放射線肺炎や食道炎などの有害事象の危険性を考慮すると，局所のみの照射野でよいと述べている[15]。最近ではHayakawaら[6]，Cheungら[2]も局所照射野のみでよいとする同様の報告を行っている。

近年FDG-PETの登場により，異常影の良悪性の鑑別診断のみならず，病期診断についても有用性が報告されている。FDG-PETは肺癌の病期診断において感度が80～90%，特異度が90%以上とCTに比較して優れている[21)22)]。MacManusらは手術不能のために放射線治療の対象となった153症例にPETを行い，22%の症例に照射野の拡大が必要になったと述べている[23]。今後，I期非小細胞肺癌に対する治療方針および放射線治療における照射野を決定する際に，CTだけでなくPETの役割が重要となっていくと予想される。

### 6) 有害事象

I期非小細胞肺癌における放射線治療の対象には，高齢者および肺や心疾患などの合併症による手術不能例が多いが，ほとんどの報告で重篤な有害事象の頻度は0～2%と低い。領域リンパ節を含めた照射野を用いている場合でも，有害事象の頻度は同様に低い。肺癌に対する放射線治療の際に最も問題となる有害事象は放射線肺炎であるが，これは照射容積と線量に大きく影響をうける。つまり，I期非小細胞肺癌に対しては領域リンパ節を照射野に含めたとしても，60 Gy前後の線量であれば，重篤な有害事象の発現は極めて少ないと考えられる。また線量計算の際に，肺の密度補正の有無によって実際の線量に10～20%程度の差違が生じると考えられるが，従来の報告の多くは密度補正をしていないため実際の線量より少ないと予想される。したがって，原発腫瘍のみに限局した小さな照射野であれば，安全に線量を70 Gy以上に増加することができると考えられる。

## 3 新しい照射方法

### 1) 分割方法の工夫

放射線治療の効果は1回線量，分割回数，総線量，照射期間などの因子によって規定される。多くの報告では，1回線量1.8～2.0 Gy，30～35分割，60～70 Gy/6～7週の照射方法で治療されている。これらの因子を変更することによって，照射効果の改善を目的とした研究が報告されている。

Slotmanらは，48 Gy/12回（2.5週）の小分割照射法を用いて，I期非小細胞肺癌31症例に治療を行い，生存期間中央値33カ月，3年全生存率は42%，原病生存率は76%であった[24]。領域リンパ節への予防照射は施行していない。Cheungらも同様の小分割照射法を用いて33症例に治療を行った[25]。領域リンパ節への転移を認めた4症例が含まれている。経過観察期間は短いが，生存期間中央値22.6カ月，2年全生存率は46%，原病生存率は54%であり，従来の照射方法より優れていたと報告している。同じ照射方法ではあるが，両者の治療成績には差違を認める。これは前者が5 cmを越える腫瘍径の症例が6%だけであったのに対して後者は26%であったこと，そしてリンパ節転移症例を対象に含んでいたことなどが大きな理由と考えられる。また，いずれの報告でも重篤な有害事象は認めていない。

1回1.5 Gyを1日3回，12日間連続で合計54 Gyを照射する加速多分割照射法であるcontinuous, hyperfractionated, accelerated radiotherapy (CHART) と，1日1回2 Gy，総線量60 Gy/6週間の通常分割照射法との比較試験が行われた[26][27]。多くは局所進行癌を対象としているが，I-IIA期における2年全生存率は通常分割照射法が24%であったのに対し，CHARTでは37%と優れていた。

### 2) 定位放射線照射技術の導入

脳内病変に対する定位放射線照射が普及しているが，この技術を肺腫瘍に応用した照射方法が日本を中心に開発されつつある。呼吸性移動を伴う肺の腫瘍に対して，精度の高い治療を行うために施設毎にさまざまな工夫がなされている。Uematsuらは，fusion of CT and linear accelerator (FOCAL) unit

と呼ばれる，CTとリニアックを共有寝台とともに同室設置した治療装置を用いて，I期非小細胞肺癌に対して50～60 Gy/5～10回の定位放射線治療を行った[28]。3年の全生存率は66%，原病生存率は88%であり，局所再発は1例も認めなかった。Nagataらは，stereotactic body frameと呼ばれる専用固定具を用いて，T1N0の16症例に48 Gy/4回の定位放射線治療を行った[29]。全例に局所制御が得られ，2年無病生存率が73%，2年全生存率は79%であった。いずれの報告も重篤な有害事象を認めなかった。五味らも同様の固定具を用いて3 cm以下の転移性腫瘍を含む肺腫瘍62病変に対して定位放射線治療を行い，2年局所制御率が72%であったと報告している[30]。しかし，この照射方法は1回線量が多く照射野も比較的小さいため，治療システムのより高い精度管理が要求され，安易に導入するべきではない。

## 4 おわりに

I期非小細胞肺癌の症例で放射線治療の対象となるのは，高齢や全身状態不良といった手術不能例が含まれることが多い。文献的には放射線治療の成績は，他病死の頻度が高いとはいえ必ずしも満足すべきものではない。しかし，比較的サイズの小さい腫瘍であれば(3～4 cm以下) 5年全生存率が25～30%は期待できる。

SibleyはI期非小細胞肺癌に対する放射線治療についてその優れたレビューのなかで次のようにまとめている[15]。

1) 一般的な60～70 Gyの外部照射におけるおおよその治療成績は，5年全生存率が15%，他病死が25%である。30%は遠隔転移で死亡するが，30%は局所単独再発後に死亡する。

2) 治療後の再発のうち50%は局所再発単独であり，領域リンパ節のみへの再発率は5%以下である。また，グレード3以上の毒性の出現率は5%以下である。

3) 局所制御率および生存率改善のために投与線量の増加が必要である。

新たな試みとして加速多分割照射法や小分割照射法による治療成績の改善が報告されている。また，日本を中心に定位放射線照射技術を応用した治療法が開発され，その初期治療成績は良好である。しかし，この照射方法は照射技術や分割方法などが施設毎に異なり，報告されている症例数も少ないことから，有用性を確認するためにはさらに多施設参加による臨床試験を進めていく必要がある。

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# Automated preparation of hypoxic cell marker [$^{18}$F]FRP-170 by on-column hydrolysis

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**Abstract**

An automated synthesis for the preparation of the novel hypoxic cell marker, [$^{18}$F]FRP-170 3, [$^{18}$F]1-[2-fluoro-1-(hydroxymethyl)ethoxy]methyl-2- nitroimidazole, was developed using an on-column basic-hydrolysis step. The $^{18}$F-labeled protected intermediate 2 was retained on a Sep-Pak Plus C18 cartridge and, in the same cartridge at room temperature, hydrolyzed by NaOH for deacetylation to give [$^{18}$F]FRP-170. The elution method from the cartridge was optimized for direct injection of the crude product into an HPLC column. Thus, [$^{18}$F]FRP-170 was prepared in 20–30% decay-corrected radiochemical yield within 60 min.


*Keywords:* F-18; Hypoxic cell marker; FRP-170; Fluoromisonidazole; Solid phase extraction; On-column; Automated synthesis

## 1. Introduction

Hypoxia refers to any condition of inadequate supply of oxygen to tissues, and is often observed in ischemic or tumor tissue. In hypoxic cells 2-nitroimidazoles are known to be reduced further than in normal cells to give more reactive products to be bound to cell components (Nunn et al., 1995). Consequently, labeled 2-nitroimodazoles are expected to be a good imaging probe for hypoxic cells and thus tumors. This was first demonstrated by $^{18}$F-labeled fluoromisonidazole ([$^{18}$F]FMISO) (Jerabek et al., 1986), and later on by several other potential analogs such as [$^{18}$F]fluoroerythronitroimidazole (Yang et al., 1995), [$^{18}$F]fluoroetanidazole (Tewson, 1997) and [$^{18}$F]EF5 (Dolbier et al., 2001).

On the grounds that RP-170, 1-[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl-2-nitroimidazole, had comparable reduction potential and radiosensitizing activity to FMISO but lower neurotoxicity (Murayama et al., 1989), the new [$^{18}$F]fluorinated derivative of PR-170, [$^{18}$F]FRP-170 3, [$^{18}$F]1-[2-fluoro-1- (hydroxymethyl)ethoxy]methyl-2- nitroimidazole, was developed (Wada et al., 2000). The preliminary results showed this tracer to be a good PET agent for visualizing the ischemic but viable myocardium (Kaneta et al., 2002). Clinical application of this promising hypoxic cell marker is now expected.

Routine preparation of PET radiopharmaceuticals for clinical diagnosis requires efficient, reproducible and automated synthesis procedures. Unfortunately, quite often a procedure originally developed for a manual radiosynthesis is not directly adaptable to automation, and time-consuming efforts are required to be modified and mostly simplified in order to achieve a successful

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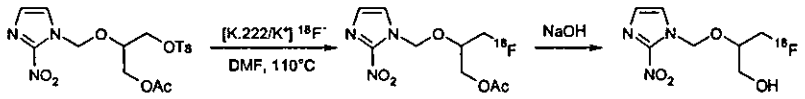


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Fig. 1. Synthesis scheme of [$^{18}$F]FRP-170 from [$^{18}$F]fluoride.

automation. As shown in Fig. 1, the radiosynthesis of [$^{18}$F]FRP-170 consisted mainly of three steps: [$^{18}$F]fluorination, deprotection by hydrolysis and purification by HPLC. The aim of this study was to simplify and optimize the last two steps by introducing a solid-phase-supported basic hydrolysis (on-column hydrolysis).

## 2. Materials and methods

All chemicals and solvents were of high grade from Aldrich Chem. Co., Merck Co. and Wako Pure Chem. Co., while RP-170 and FRP-170 were generous gifts from POLA Chem. Ind. The precursor **1**, 1-[2-(toluene-4-sulfoxy)-1-(acetoxymethyl)ethoxy]-methyl-2-nitroimidazole, was prepared from RP-170 as described previously (Wada et al., 2000). No-carrier-added $^{18}$F-fluoride ([$^{18}$F]F$^-$) was produced by the $^{18}$O(p, n)$^{18}$F reaction on enriched [$^{18}$O]$H_2O$ with the HM-12 cyclotron (Sumitomo Heavy Industries) at CYRIC.

Quantitative analysis of FRP-170 and [$^{18}$F]FRP-170 was carried out by HPLC on a C18 column (Waters Puresil, 4.6 × 150 mm$^2$, mobile phase: MeCN/$H_2O$ = 7/93 or 25/75, flow rate = 2.0 mL/min).

### 2.1. Radiosynthesis

The [$^{18}$F]F$^-$ was separated from the irradiated target with a Sep-Pak Light Accell Plus QMA cartridge (Waters) that had been washed in advance with $K_2CO_3$ (0.5 M, 10 mL) followed by $H_2O$ (5 mL). The trapped [$^{18}$F]F$^-$ was eluted with a solution of Kryptofix 222 (K.222, 20 mg) and $K_2CO_3$ (33 mM, 0.6 mL) in MeCN (2 mL) and the eluate was evaporated to dryness by azeotropic distillation with a He flow (300–400 mL/min). The drying was guaranteed by repeating the azeotropic distillation three more times with 1 mL of dry MeCN. To the residue was added a solution of the precursor **1** (2 mg) in DMF (0.7 mL) and the mixture was heated at 110 °C for 3 min. After cooling the solution was diluted with HCl (0.05 M, 5 mL) and passed through a Sep-Pak Plus C18 Environmental Cartridge (Waters) which had been activated by washing with EtOH (5 mL) and $H_2O$ (5 mL). The cartridge was rinsed with $H_2O$ (5 mL) and then filled with NaOH (0.1–1 M, 2 mL) to carry out the on-column hydrolysis. The cartridge was then washed with $H_2O$ (1 mL) and the hydrolyzate eluted with a mixture of MeCN, AcOH and $H_2O$. The eluate was directly injected onto an HPLC C18 column (YMC A-324, 10 × 300 mm, mobile phase: MeCN/$H_2O$ = 12/88, flow rate = 4.0 mL/min, wavelength = 280 nm) through an HPLC injector (volume of a sample loop = 2 mL). The fraction containing the desired product was collected at 13–14 min.

### 2.2. Optimization of basic hydrolysis

The condition of on-column hydrolysis was optimized by varying the concentration of NaOH and the reaction time. The protected [$^{18}$F]FRP-170, purified by solid-phase extraction (SPE) as described above, was dissolved in $H_2O$ (10 mL). A small portion of this solution (0.3–0.5 mL) was diluted with $H_2O$ (5 mL) and the whole solution was passed through an activated Sep-Pak Plus C18 Environment cartridge (Waters). After filling different concentrations of NaOH (0.1–1 M) the Sep-Pak content was allowed to react at room temperature for different times (1–10 min). The cartridge was then eluted with MeCN/$H_2O$ (50/50, 3 mL) through an IC-H Plus cartridge (Alltech) for neutralization. The hydrolysis yields were determined by HPLC analysis.

Basic hydrolysis in a homogeneous solution was also carried out for comparison. A small portion of the protected [$^{18}$F]FRP-170 solution was added to NaOH (0.01–1 M) and the reaction carried out at either room temperature or 50 °C for various times. The reaction products were also analyzed by HPLC.

### 2.3. Selection of SPE eluents for HPLC separation

In order to investigate the effect of polarity of the SPE eluents on the preparative-HPLC separation of [$^{18}$F]FRP-170, both [$^{18}$F]FRP-170 and a non-radioactive by-product eluted nearby were collected together from the HPLC column and evaporated to dryness. The residue was dissolved in $H_2O$ (2 mL). Appropriate portions of this solution were added to MeCN to get MeCN/$H_2O$ ratios ranging from $\frac{10}{90}$ to $\frac{80}{20}$ while maintaining the volume fixed at 2 mL. Each solution was injected onto the column and the separation was recorded for radioactivity and UV.

Moreover, since the solution loaded into the HPLC loop was just the eluate from the C18 cartridge, the effect of the solvent polarity on the elution efficiency was also studied. Thus, FRP-170 (0.1 mg) dissolved in $H_2O$ (2 mL) was passed through a Sep-Pak C18 cartridge and