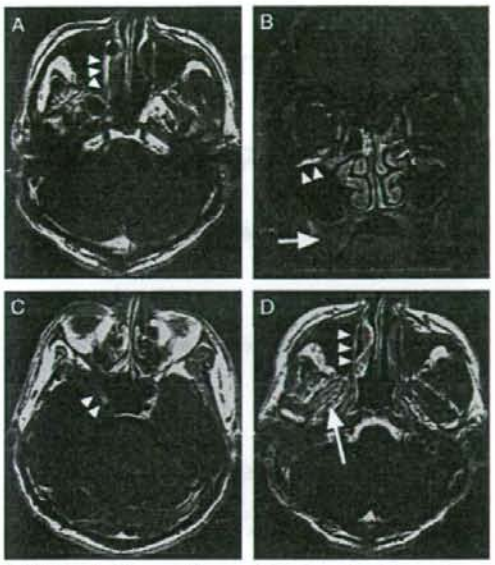

FIGURE 1. A 62-year-old man with adenoid cystic carcinoma of the right trigeminal ganglion received adjuvant stereotactic radiotherapy (33 Gy) to the right Meckel's cave. Afterward, the patient was repeatedly treated with radiotherapy because of recurrence as a form of perineural tumor extension (PTI); external or stereotactic irradiation was delivered to the bottom of the right temporal lobe (33 Gy), the right skull base (50 Gy) and to the right orbit (50 Gy) followed by boost irradiation (14 Gy). Four months after treatment, magnetic resonance (MR) imaging revealed development of PTI in the posteromedial portion of the right maxillary sinus (A and D, arrowheads) and the right palate (B, arrow). In addition, some lesions still had contrast enhancement even after radiotherapy: inferior portion of the right orbit along the pathway of the infraorbital nerve (B, arrowheads), maxillary division of trigeminal nerve along the right foramen rotundum (C, arrowheads), and fat pad around the right pterygoid muscle indicating retrograde spread along the mandibular division of the trigeminal nerve (D, arrow).

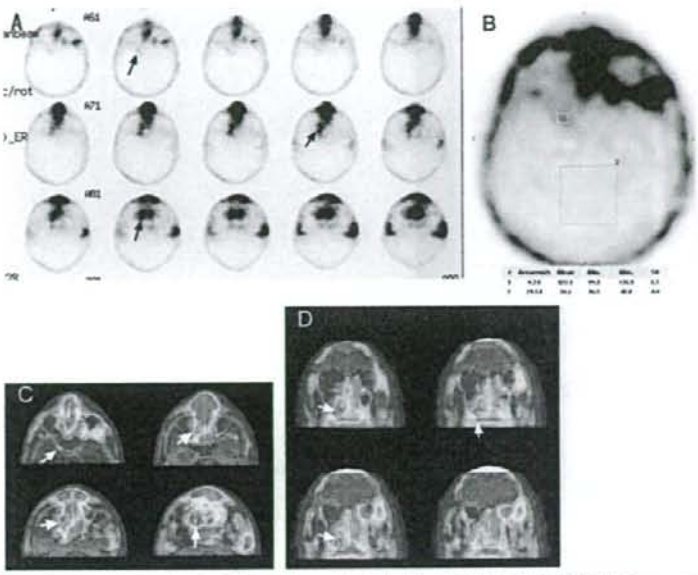

FIGURE 2. After informed consent was obtained from the patient, thallium-201 (Tl-201) SPECT/CT was performed to evaluate tumor extent and viability after therapy. SPECT showed abnormal uptake near the right Meckel's cave and posteromedial portion of the right maxillary sinus extending into the right palate (A, arrows). The count ratio between the former lesion and normal brain was 4.1 (B). SPECT/CT image fusion technique was reported previously.[1] Fusion images showed precise location of the abnormal uptake sites (C and D, arrows). Coronal SPECT/CT images show abnormal uptake extending from the medial portion of the right maxillary sinus to the right palate (D, arrows). No pathologic uptake is noted around the right orbit.

There are some case reports concerning application of nuclear imaging in the evaluation of PTI. Fluorine-18 fluorodeoxyglucose (FDG) PET fused with CT has been useful to detect PTI in patients with squamous cell carcinoma of the lip.[2,3] Fosko et al[4] reported a patient with basal cell carcinoma of the head and neck in which FDG PET failed to detect PTI. The absence of Tl-201 uptake by bony structures such as the skull base contributes to the high tumor-to-nontumor ratio,[5] which may enhance usefulness of SPECT/CT image fusion for precise localization of viable PTI.

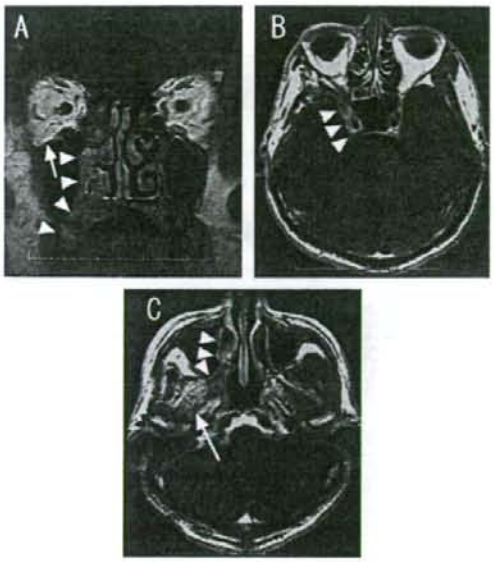

FIGURE 3. MR imaging performed 4 months after the MR and SPECT studies showed marked thickening with contrast enhancement from the medial portion of the right maxillary sinus to the right palate (A and C, arrowheads). Disease progression was also noted in the maxillary division of the trigeminal nerve along the right foramen rotundum (B, arrowheads). By contrast, there was no evidence of disease progression in the right infraorbital nerve (A, arrow) and around the right pterygoid muscle (C, arrow). MR imaging is of great value in the evaluation of head and neck cancers,[6] although its possible limitation of post-therapeutic evaluation suggests the need for nuclear imaging such as positron emission tomography (PET) and SPECT.[7,8]

Ann Nucl Med (2008) 22:207–213
DOI 10.1007/s12149-007-0095-y

ORIGINAL ARTICLE

Accumulation of gallium-67 within mature and immature teratoma in pediatric patients: investigation for the uptake mechanism

**Etsuo Kunieda · Hiroko Hara · Yukihiko Morikawa
Seiichi Hirobe · Shoichiro Kamagata · Atsushi Kubo**

Received: 21 August 2007 / Accepted: 3 December 2007

Abstract
Objective We encountered cases of mature and immature teratoma with positive uptake of ^{67}Ga. The objective of this study is to investigate the mechanism of ^{67}Ga accumulation within mature and immature teratomas by comparing the findings of gallium scan, computed tomography (CT), and autoradiography of surgical specimens with the pathological findings.
Methods The subjects comprised 14 children who underwent surgical resection for intra-abdominal mature and immature teratomas, which were histologically proved to be of the mature and immature subtype. Their age ranged from 24 days to 14 years. The origins of the mature teratomas consisted of seven ovaries including one bilateral case, two retroperitoneal, and two sacrococcygeal regions. The origins of the immature teratomas were retroperitoneum in two cases, an ovary and a sacrococcygeal region. Complete surgical excision was feasible in all children. They underwent both gallium scan and CT prior to surgery. Single-photon emission computed tomography was added in some cases. For two gallium-positive cases, radiography and scintigraphy (autoradiography) of the resected specimen were performed.
Results Of the 14 children, 5 (one with immature and four with mature subtype) showed positive ^{67}Ga uptake within tumors, which originated from the retroperitoneum in the 3 boys, and from the ovary in the 2 girls. All had typical CT findings of teratoma, including calcifications, fat components, cystic areas, and solid parts. ^{67}Ga accumulation in the four mature teratomas appeared discretely strong, and was considered to correspond with intralesional calcifications. However, in the remaining one immature teratoma, the gallium distribution was diffuse within the tumor. The comparison between radiography and autoradiography of the resected mature teratomas confirmed the correlation between the intralesional calcifications and areas of ^{67}Ga accumulation.
Conclusions A high-uptake ratio of ^{67}Ga in benign teratoma was indicated. A close correlation between gallium scan and CT helps to ascertain whether ^{67}Ga uptake results from malignant and/or immature elements, or mature tissue components.

Keywords Teratoma · Benign tumor · Calcification · ^{67}Ga

E. Kunieda
Department of Radiology, Tokyo Metropolitan Kiyose Children's Hospital, Kiyose, Tokyo, Japan

E. Kunieda (✉) · A. Kubo
Department of Radiology, Keio University, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: kunieda-mi@umin.ac.jp

H. Hara
Department of Radiology, Kawaguchi Municipal Hospital, Kawaguchi, Saitama, Japan

Y. Morikawa
Department of Pathology, Tokyo Metropolitan Kiyose Children's Hospital, Kiyose, Tokyo, Japan

S. Hirobe · S. Kamagata
Department of Surgery, Tokyo Metropolitan Kiyose Children's Hospital, Kiyose, Tokyo, Japan

Introduction

Teratoma is the commonest congenital tumor that arises from totipotent somatic cells or premeiotic germ cells. The origin, biological activity, and histological charac-

teristics of teratomas are diverse, and tumors are divided into three categories, namely, mature teratoma, immature teratoma, and teratoma with malignant components. Malignant teratoma accounts for 3% of all childhood malignancies [1]. Immature teratoma is associated with an increased incidence of malignancy, whereas mature teratoma falls at the benign end of the spectrum. However, the prognostic importance of immature elements should be individually evaluated in the context of the maturity of patients, whereas even mature teratomas with a high degree of fetiformity occasionally recur. Therefore, we still need to investigate important prognostic factors of teratomas on clinical, radiological, and histological grounds.

Radionuclide imaging using ^{67}Ga citrate (gallium scan) has been widely employed to detect both malignant and inflammatory lesions. However, very little is known about the role of gallium scan in decision-making for patients with teratomas. A few studies have reported low-positive uptake rates of ^{67}Ga within benign teratomas [2–4], but most did not specify the subtype of the teratomas. As far as we know, mature teratomas with a positive uptake of ^{67}Ga have not been reported. The positive uptake of ^{67}Ga has been believed to indicate the presence of immature or malignant components. Moreover, it is often considered that ^{67}Ga does not accumulate in most of the benign tumors in the absence of other special reasons such as inflammation.

Inconsistent with the current belief, we encountered cases of mature and immature teratoma with positive uptake of ^{67}Ga. This experience led us to investigate the mechanism of ^{67}Ga accumulation within benign teratomas by comparing the findings of gallium scan with sectional imaging, computed tomography (CT), and autoradiography of surgical specimens with pathological findings.

Materials and methods

This study was approved by our institutional review board, and an informed consent regarding the use of the specimens for the study was obtained from the guardians of the patients. Subjects comprised 14 children, who underwent surgical resection for intra-abdominal teratomas, which were histologically proven to be of mature or immature teratoma, at the Tokyo Metropolitan Kiyose Children's Hospital between January 1995 and August 2001 (Table 1). Their age ranged from 24 days to 14 years (mean age 9 years 11 months). The origins of the mature teratomas were seven ovaries including one bilateral case, two retroperitoneal, and two sacrococcygeal regions (seven girls and three boys). Regarding immature teratomas, their origins were the retroperitoneum in two cases, an ovary and a sacrococcygeal region. Complete surgical excision was feasible in all children, and they have not shown any recurrence to date. All children underwent both gallium scanning and CT prior to surgery. Gallium scan images were obtained 48–72 h following intravenous injection of ^{67}Ga citrate (37–111 MBq, adjusted for the children's age, weight, and other clinical conditions) using a gamma camera (PRISM-200XP; Picker International, Cleveland, OH, USA) with a medium-energy collimator. Energy windows were set to 93 keV ± 20% and 185 keV ± 15% in consideration of the photopeaks of ^{67}Ga. Spot views focusing on the area of disease involvement as well as whole-body anterior and posterior views were obtained. Additional single-photon emission computed tomography (SPECT) images were acquired for planar-positive cases at 3° angular increments of the camera rotation, with an acquisition time of 20 min.

For gallium-positive cases, radiography and scintigraphy (autoradiography) of the resected specimen were

Table 1 Cases

Patient no.	Age at resection	Sex	Origin	Pathology	^{67}Ga uptake
1	25 days	F	Sacrococcygeal	Immature	−
2	47 days	F	Retroperitoneum	Immature	−
3	5 months	M	Retroperitoneum	Immature	+ (diffuse)
4	14 years	F	Ovary, right	Immature	−
5	52 days	M	Retroperitoneum	Mature	+
6	3 months	F	Sacrococcygeal	Mature	−
7	4 years	F	Sacrococcygeal	Mature	+
8	5 years	F	Ovary, right	Mature	−
9	5 years	F	Ovary, right	Mature	−
10	6 years	F	Ovary, left	Mature	+
11	14 years	F	Ovary, left	Mature	−
12	11 months	M	Retroperitoneum	Mature cystic	+
13	2 years	M	Sacrococcygeal	Mature cystic	−
14	5 years	F	Ovary, right	Mature cystic	−

performed within 3 days following the resection. Radiography was performed with 40 kVp X-rays. Autoradiography was performed using the same gamma camera as used for the clinical studies, with the same energy window. The acquisition of data was carried out using the same collimator, and the specimen was placed as close as possible to the collimator. The acquisition was continued until the count of the image reached approximately 70 counts per pixel.

Computed tomography images were obtained with a single-detector row CT scanner (HiSpeed Advantage SG; GE Medical Systems, Milwaukee, WI, USA). Helical scanning was utilized with 5-mm collimation, 5 mm/s table speed, and 5-mm reconstruction in children younger than 6 years of age, and with 7-mm collimation, 7 mm/s table speed, and 7-mm reconstruction in those 6 years of age and over.

Results

Of the 14 children, 5 (one immature and four mature subtypes) had positive ^{67}Ga uptake within tumors that originated from the retroperitoneum in 3 boys and from the ovary in 2 girls (Table 1). All the subjects had typical CT findings of teratoma including calcifications, fat components, cystic areas, and solid parts. ^{67}Ga accumulation in the four mature teratomas was discrete and strong (Figs. 1, 2, 3) and corresponded with intralesional calcifications. However, in the remaining one immature teratoma, the gallium distribution was diffuse in the tumor (Fig. 4). In this case, the CT scan did not reveal localized or prominent calcification. Calcifications were found in all cases except one mature (case 5) and one immature teratoma (case 1) at least in some part of the teratoma lesions. The cases without any calcification had no gallium uptake.

X-ray radiography and autoradiography (scintigraphy of the specimen) were obtained for the surgical specimens in two gallium-positive mature teratomas. In the other cases, the periods between the gallium injection and the operation were too long to obtain sufficient radioactivity from the surgical specimens. The comparison between X-ray radiography and autoradiography confirmed the correlation between the intralesional calcifications and areas of ^{67}Ga accumulation (Figs. 2, 3). A histological examination elucidated the presence of bone marrow tissues within the calcified areas.

Discussion

Use of positron emission computed tomography imaging has become increasingly widespread. In particular, 18F-fluoro-2-deoxy-D-glucose is now commonly used for the detection of malignancies [5–7]. Although gallium scintigraphy has been used to detect and localize neoplasms [8–12], its current role in surveying for malignancies has diminished. Nevertheless, it is still valuable for radiologists or nuclear medicine physicians to know that the gallium agent accumulates in benign teratomas with a high incidence ratio and to know the mechanism of gallium uptake in teratomas.

^{67}Ga concentrates in inflammatory or mitotically active tissues, including malignant tumors [13–18], as well as in the liver, bone, bone marrow, nasopharynx,

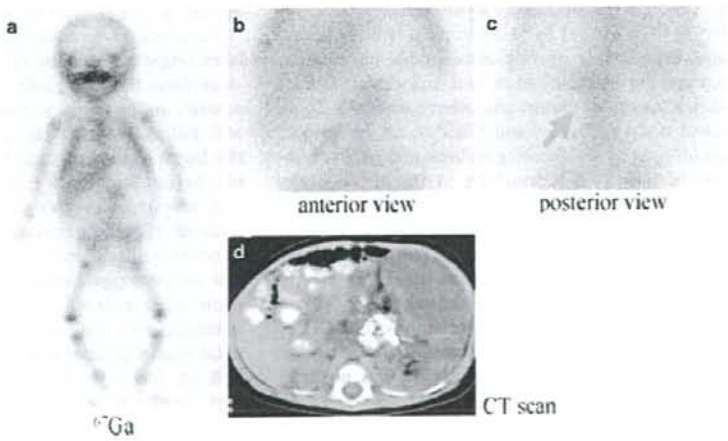

Fig. 1 A 52-day-old boy with a mature teratoma in the retroperitoneum (case 5). Gallium scintigraphy (**a**–**c**) reveals positive uptake in the mid-abdomen (*arrows*). Computed tomography (CT, **d**) shows a large retroperitoneal teratoma consisting of calcification, fat, cystic, and solid components. A calcification correlated with the area of gallium accumulation is demonstrated

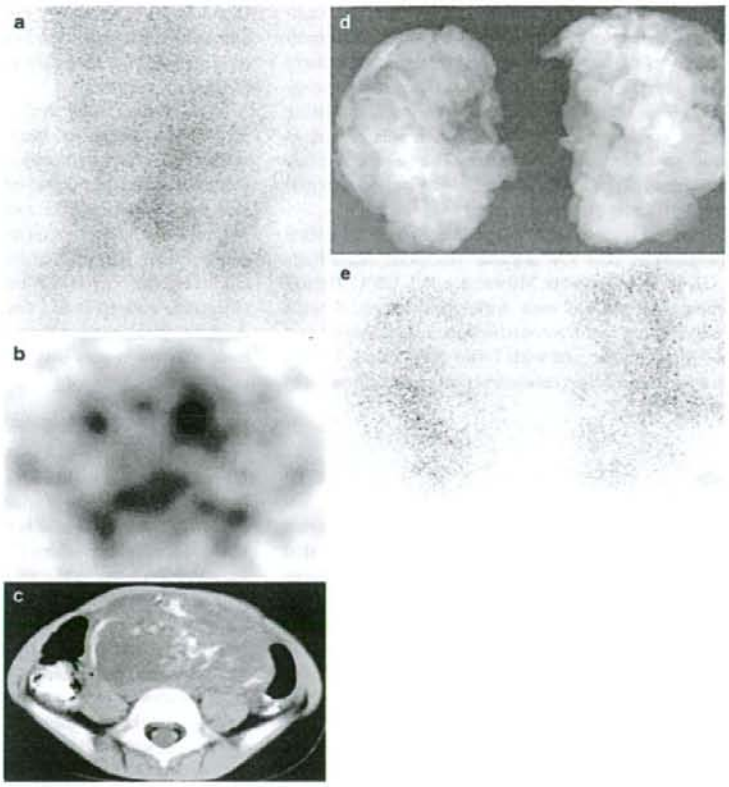

Fig. 2 A 4-year-old girl with a mature teratoma in the ovary (case 7). The gallium scintigraphy of the abdomen (**a**) demonstrates ^{67}Ga uptake in the lower abdomen. ^{67}Ga single-photon emission computed tomography (SPECT) image (**b**) at the same level as the CT (**c**) indicates ^{67}Ga uptake corresponding with the area of calcification. Specimen (cut to half) radiograph (**d**) and scintigraphy (**e**) demonstrate calcification correlating with the area of ^{67}Ga accumulation

lacrimal gland, thymus, breast, colon, and other organs [19]. Although the mechanism of intratumoral accumulation of ^{67}Ga has yet to be determined with certainty, animal experiments provide considerable information regarding the biodistribution and subcellular fate of ^{67}Ga in a variety of tumors and other tissues [20–22]. A classical study by Dudley and Maddox, on the basis of autoradiography and focusing on bone tumors first demonstrated that ^{67}Ga accumulates in the metabolically active parts of the bone [23]. Modern studies elucidate preferential uptake of ^{67}Ga in nuclei of osteoclasts at sites of rapid new bone formation [24] and in bone marrow lymphocytes [25]. Gallium uptake in heterotopic and metastatic calcifications has also been demonstrated [26, 27]. The transferrin receptors (TfR/CD71) play an important role in the mechanisms of ^{67}Ga uptake by tumor cells. CD71 binds transferrin and mediates uptake of iron [28]. The receptors are expressed on marrow stromal cells from bone marrow [29] as well as on activated T and B lymphocytes, but are not expressed on resting lymphocytes or mature erythrocytes.

Teratomas are embryonic neoplasms that develop from totipotent somatic cells or premeiotic germ cells when these immature cells escape from developmental control, and give rise to more or less organoid masses with cell components derived from all three blastodermic layers (ectoderm, endoderm, and mesoderm). Their histological features are therefore heterogeneous, and they may include cystic or solid areas with organoid patterns as well as mature or immature components. Teratomas in children commonly occur in the ovary and sacrococcygeal region, but they are also found in many other anatomic regions [30]. Occult malignancy (teratoma with yolk sac elements) is common in neonatal sacrococcygeal teratomas, and detection of such yolk sac foci is particularly important [31]. Teratomas with immature elements are at risk of malignant transformation.

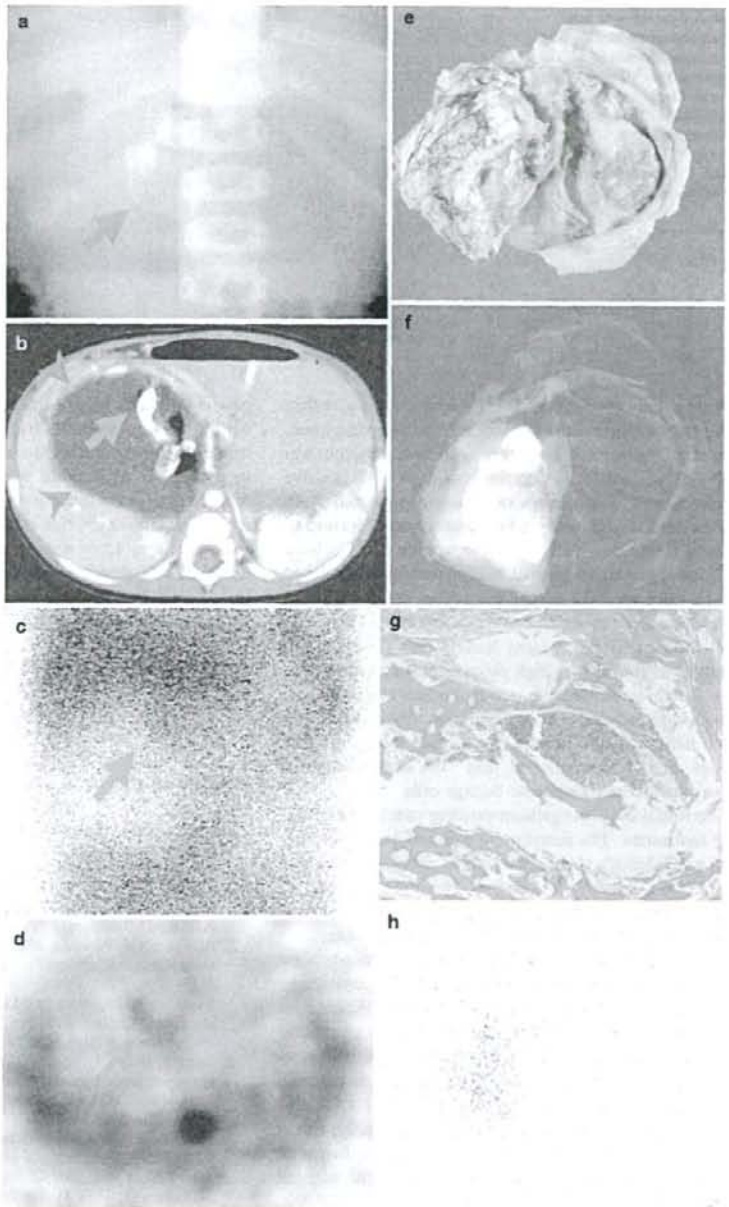

Fig. 3 An 11-month-old boy with a mature teratoma in the retroperitoneum (case 12). Abdominal radiograph (**a**) shows calcification in the mid-abdomen (*arrow*). CT (**b**) reveals a calcified component (*arrow*) and a cystic lesion (*arrowheads*). ^{67}Ga anterior image (**c**) and SPECT image (**d**) at the same level of the CT (**b**) show ^{67}Ga uptake corresponding with the area of calcification. Photograph (**e**), radiography (**f**), and autoradiography (**h**) of the specimen demonstrate amorphous calcification (ossification) corresponding with the area of ^{67}Ga accumulation. Pathology (**g**) reveals bone marrow tissue and bone in the area of calcification

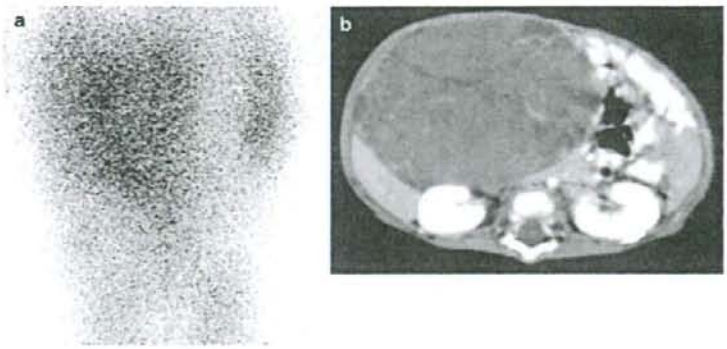

Fig. 4 A 5-month-old boy with an immature teratoma in the retroperitoneum (case 3). The gallium scintigraphy of the abdomen (**a**) demonstrates ^{67}Ga uptake in the upper abdomen overlapped with the liver uptake. CT images (**b**) of the mid of the tumor

Anecdotal experiences of ^{67}Ga accumulation within malignant and immature teratomas have been described. However, there have been few reports on the clinical utility of gallium scan for the lesion. A low positive uptake rate of ^{67}Ga within teratomas was reported [2–4], but the authors did not specify the subtype of teratomas. Mature teratomas with a positive uptake of ^{67}Ga have not been reported. In general, benign tumors are believed not to take up ^{67}Ga unless particular factors such as inflammation or malignant components exist. This belief was disputed by the present finding that positive ^{67}Ga uptake was found in a high proportion of mature teratomas. We confirmed the correspondence between the uptake and intralesional ossifications. The ossifications were histologically proven to include bone marrow tissues, and it is postulated that ^{67}Ga accumulated in bone marrow hematopoietic lineage cells.

We found only one gallium-positive case in the immature teratomas. The sample size was small and not adequate to identify the accumulation mechanism of the gallium in the immature subtype. However, the case we encountered apparently had a different accumulation pattern of gallium from that of mature teratomas.

As is well known, mature or immature teratomas are very often are associated with calcified components. In our experience, all but two cases had calcification in some part of the lesion. Although the gallium accumulations found in our study were associated with intralesional calcifications or ossifications, not all the calcified components had gallium uptake. The reason for this inconsistency is beyond the scope of this study, but it might be partially explained by multifarious forms of calcification in teratomas (for example, with/ without bone marrow tissue).

In conclusion, we reported gallium uptake in benign teratomas for the first time. Meticulous correlation between gallium scans and other imaging modalities, particularly CT, helps to ascertain whether ^{67}Ga uptake within teratomas results from malignant and/or immature elements or mature tissue components. It would be intriguing to investigate whether ^{67}Ga uptake within mature teratomas represents increased biological activity, i.e., an enhanced risk of recurrence. SPECT and CT fusion techniques or a more advanced modality such as a SPECT/CT device would be helpful to facilitate more detailed analysis of the correlation of gallium uptake and morphological changes in CT.

Acknowledgments The authors are grateful to Dr. Gen Nishimura and Dr. Katsumi Ishii for their contribution to revisions of the manuscript and clinical work.

References

1. Brodeur GM, Howarth CB, Pratt CB, Caces J, Hustu HO. Malignant germ cell tumors in 57 children and adolescents. Cancer 1981;48:1890–8.
2. Lepanto PB, Rosenstock J, Littman P, Alavi A, Donaldson M, Kuhl DE. Gallium-67 scans in children with solid tumors. AJR Am J Roentgenol 1976;126:179–86.
3. Paterson AH, Peckham MJ, McCready VR. Value of gallium scanning in seminoma of the testis. Br Med J 1976;1: 1118–21.
4. Sauerbrunn BJ, Andrews GA, Hubner KF. Ga-67 citrate imaging in tumors of the genito-urinary tract: report of cooperative study. J Nucl Med 1978;19:470–5.
5. Basu S, Nair N, Shet T. Detection of unsuspected metachronous second primary malignancy giving rise to supposed "non-iodine avid metastasis" in differentiated thyroid carcinoma. Clin Nucl Med 2007;32:655–8.
6. Israel O, Kuten A. Early detection of cancer recurrence: 18F-FDG PET/CT can make a difference in diagnosis and patient care. J Nucl Med 2007;48 Suppl 1:28S–35S.
7. Nakahara T, Fujii H, Ide M, Mochizuki Y, Takahashi W, Yasuda S, et al. F-18 FDG uptake in endometrial cancer. Clin Nucl Med 2001;26:82–3.
8. Weiner M, Leventhal B, Cantor A, Wimmer R, Berry DL, Cook B, et al. Gallium-67 scans as an adjunct to computed

tomography scans for the assessment of a residual mediastinal mass in pediatric patients with Hodgkin's disease: a Pediatric Oncology Group study. Cancer 1991;68:2478–80.
9. Kosuda S, Aoki S, Suzuki K, Nakamura H, Nakamura O, Shidara N. Primary malignant lymphoma of the central nervous system by Ga-67 and TI-201 brain SPECT. Clin Nucl Med 1992;17:961–4.
10. Connolly LP, Drubach LA, Ted Treves S. Applications of nuclear medicine in pediatric oncology. Clin Nucl Med 2002; 27:117–25.
11. Feldges A, Wagner HP, Bubeck B, Kehrer B, Ries G, Schmid U, et al. Recurrent mediastinal mass in a child with Hodgkin's disease following successful therapy: a diagnostic challenge. Pediatr Surg Int 1997;12:613–7.
12. Nakahara T, Togawa T, Nagata M, Kikuchi K, Hatano K, Yui N, et al. Detection and chemoradiotherapeutic evaluation of advanced esophageal squamous cell carcinoma using gallium-67 SPET: a preliminary study. Eur J Nucl Med Mol Imaging 2002;29:1072–7.
13. Edwards CL, Hayes RL. Scanning malignant neoplasms with gallium 67. JAMA 1970;212:1182–91.
14. Higasi T, Nakayama Y, Murata A, Sugiyama M, Nakamura K. Clinical evaluation of 67 Ga-citrate scanning. J Nucl Med 1972;13:196–201.
15. Lavender JP, Lowe J, Barker JR, Burn JI, Chaudhri MA. Gallium 67 citrate scanning in neoplastic and inflammatory lesions. Br J Radiol 1971;44:361–6.
16. Siemsen JK, Sargent EN, Grebe SF, Winsor DW, Wentz D, Jacobson G. Pulmonary concentration of Ga67 in pneumoconiosis. Am J Roentgenol Radium Ther Nucl Med 1974;120: 815–20.
17. Hayes RL, Szymendera JJ, Byrd BL. Effect of food intake on the tissue distribution of gallium-67: concise communication. J Nucl Med 1979;20:938–40.
18. Van der Wall H, Murray IP, Jones PD, Dwyer JM. Gallium scintigraphy in AIDS. Med J Aust 1990;153:14–20.
19. Ando A, Ando I, Takeshita M, Hiraki T, Hisada K. Subcellular distribution of gallium-67 in tumor and liver. Int J Nucl Med Biol 1982;9:65–9.
20. Ito Y, Okuyama S, Sato K, Takahashi K, Sato T, Kanno I. 67 Ga tumor scanning and its mechanisms studied in rabbits. Radiology 1971;100:357–62.
21. Langhammer H, Glaubitt G, Grebe SF, Hampe JF, Haubold U, Hor G, et al. 67 Ga for tumor scanning. J Nucl Med 1972;13:25–30.
22. Larson SM, Rasey JS, Allen DR, Grunbaum Z. A transferrin-mediated uptake of gallium-67 by EMT-6 sarcoma: II. Studies in vivo (BALB/c mice): concise communication. J Nucl Med 1979;20:843–6.
23. Dudly H, Maddox G. Deposition of radiogallium (Ga-72) in skeletal tissue. J Pharmacol Exp Ther 1949;96:224.
24. Mills BG, Masuoka LS, Graham CC Jr, Singer FR, Waxman AD. Gallium-67 citrate localization in osteoclast nuclei of Paget's disease of bone. J Nucl Med 1988;29:1083–7.
25. Boxen I. Gallium accumulation in marrow lymphocytes. Clin Nucl Med 1999;24:173–6.
26. Auerbach JM, Ho J. Gallium-67 uptake in the lung associated with metastatic calcification. AJR Am J Roentgenol 1981;136: 605–7.
27. Sullivan WT, Orzel JA, Reed KD, Bower JH. Abnormal lung and liver uptake of gallium-67 and technetium-99 m MDP in hypercalcemia of lymphoma with metastatic pulmonary calcification. Clin Nucl Med 1986;11:545–8.
28. Nejmeddine F, Raphael M, Martin A, Le Roux G, Moretti JL, Caillat-Vigneron N. 67 Ga scintigraphy in B-cell non-Hodgkin's lymphoma: correlation of 67 Ga uptake with histology and transferrin receptor expression. J Nucl Med 1999;40:40–5.
29. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7.
30. Martino F, Avila LF, Encinas JL, Luis AL, Olivares P, Lassaletta L, et al. Teratomas of the neck and mediastinum in children. Pediatr Surg Int 2006;22:627–34.
31. Hawkins E, Issacs H, Cushing B, Rogers P. Occult malignancy in neonatal sacrococcygeal teratomas: a report from a Combined Pediatric Oncology Group and Children's Cancer Group study. Am J Pediatr Hematol Oncol 1993;15:406–9.

Radiotherapy and Oncology 87 (2008) 326–330
www.thegreenjournal.com

Phase III randomised trial

Efficacy of novel hypoxic cell sensitiser doranidazole in the treatment of locally advanced pancreatic cancer: Long-term results of a placebo-controlled randomised study☆

Katsuyuki Karasawa[a,*], Makoto Sunamura[b], Atsutake Okamoto[c], Kenji Nemoto[d]
Seiki Matsuno[b], Yasumasa Nishimura[e], Yuta Shibamoto[f]

[a]*Department of Radiology, Tokyo Metropolitan Komagome Hospital, Japan,* [b]*Department of Surgery, Tohoku University School of Medicine, Japan,* [c]*Department of Surgery, Tokyo Metropolitan Komagome Hospital, Japan,* [d]*Department of Radiology, Tohoku University School of Medicine, Japan,* [e]*Department of Radiation Oncology, Kinki University School of Medicine, Japan,* [f]*Department of Radiology, Nagoya City University School of Medicine, Japan*

Abstract

Novel hypoxic cell radiosensitiser doranidazole was tested for unresectable pancreatic cancer administered at intraoperative radiotherapy. Short-term survival was not different. However, difference has been observed concerning 3-year survival (doranidazole group vs. placebo; 23% vs. 0%, $p = 0.0192$). This sensitiser might be effective in improving long-term survival for pancreatic cancer.
 Radiotherapy and Oncology 87 (2008) 326–330.

Keywords: Pancreatic cancer; Radiotherapy; IORT; Hypoxic cell radiosensitiser; Doranidazole

The development of hypoxic cell radiosensitisers has continued for more than 30 years [3,6,11,17–19]. Despite all these efforts, such agents still see relatively little use, and the main reasons are twofold. First, many agents do not successfully enhance radiotherapeutic effects. Secondly, the drug itself is often toxic to certain normal tissues, due to the high value of the partition coefficient (lipid–water partition). To decrease the value of the partition coefficient, great efforts have been put in on developing new compounds for more than a decade in Japan, finally resulting in the new compound doranidazole (PR-350; Pola Chemical Industries, Kanagawa, Japan), with three hydroxyls in the nitroimidazole side chain.

Following promising results from preclinical studies [10,21], this compound was used for patients with pancreatic cancer in a phase I study to determine its safety and efficacy [23]. Pancreatic cancer is known to be radioresistant and reportedly contains hypoxic tumour cells [4]. Pancreatic cancer also represents a good target for intraoperative radiation therapy (IORT), which provides a high single dose to the tumour, but for which hypoxic cells might pose more problems because the proportion of hypoxic cells dominates in the surviving fraction. Theoretically, the addition of hypoxic cell sensitiser should allow more hypoxic radioresistant cells to be killed and thus facilitate local tumour control. The phase I study was successfully closed with no severe adverse effects, no identification of any maximum tolerable dose, and promising survival data concerning locally advanced cases (median survival time, around 12 months).

Given these promising phase I study data, a multicentre double-blind phase III randomised study was conducted to compare outcomes for IORT with or without doranidazole followed by postoperative external beam radiotherapy. The preliminary results have been already published [24]. No differences were noted in 1-year overall survival rate between groups, but longer term results tended to be better for the doranidazole group. The data have been re-analysed to include at least 2 more years of follow-up and the long-term results are reported herein.

Materials and methods

Doranidazole (PR-350)

Radiosensitiser doranidazole was synthesised at Pola Chemical Industries. Doranidazole is a 2-nitroimidazole nucleoside analogue with a $CH_2OCH(CH_2OH)CH(OH)CH_2OH$ side chain at the N1 position.

☆ Presented at 13th ECCO, held October 30th to November 3rd, 2005, Paris.

0167-8140/$ - see front matter doi:10.1016/j.radonc.2008.02.007

Study design

Study design was reported in the previous report. The study protocols were approved by the ethical committees of the involved institutions.

Endpoints:

(1) Primary endpoints were overall 1-year survival, median survival time, and safety of the drug for 14 days following IORT.
(2) Secondary endpoints were effective response rate, tumour marker values, and the volume of analgesic drugs.

Eligibility criteria and exclusion criteria were also mentioned in the previous report, and are thus mentioned only briefly.

Eligibility criteria:

(1) patients must be 20- to 75-years-old;
(2) patients must have a performance status of 0–2, projecting a survival period >3 months;
(3) tumours must be unresectable due to invasion to the arterial system or peripancreatic nerve plexus;
(4) maximal diameters of tumours must be less than that required for radiotherapy; and
(5) liver metastasis, other organ metastasis and peritoneal seeding must be absent.

Exclusion criteria:

(1) previous radio- or chemotherapy;
(2) idiosyncratic reactions to drugs, including contrast media;
(3) presence of serious cardiovascular, pulmonary, renal, or hepatic disease;
(4) concomitant active neoplasia; or
(5) any condition believed by the physician-in-charge to preclude participation in the trial.

Following written informed consent to participate in the trial was obtained from the patient who met the above criteria, patients were registered as potential candidates at the trial central office. This was a prospective, randomized, closed-label, controlled study of IOR with or without radiosensitiser doranidazole. Patients were randomized by adaptive randomization method and notified by FAX. Final eligibility was determined based on operative findings by laparotomy.

After laparotomy, a biopsy specimen from each participant was analysed to confirm diagnosis. Infusions of doranidazole or placebo were strictly controlled to obtain a suitable concentration for radiotherapy; 2000 mg/m^2 of doranidazole or placebo was infused systemically for ~25 min before administration of IORT. Ten to 40 min after the completion of doranidazole or placebo administration, the patients were carried to the radiotherapy room and received 25 Gy of IORT at the maximum dose point covering gross tumour volume (the primary tumour and enlarged lymph nodes). The energy of the electron beam was selected so that all gross tumour volume was covered by 90% isodose line. Two weeks following surgery, all patients received EBRT. The total planned dose of 40 Gy at the isocentre was delivered in 20 fractions in 4 weeks using 10~14 MV photons. The radiation fields included the clinical target volume (gross tumour volume and the celiac and superior mesenteric artery) with 1–3 cm margins. CT-based multiple-port radiotherapy techniques were employed in order to lower the dose to the spinal cord.

No additional therapy, including chemotherapy and immunotherapy, was allowed for 6 months after IORT treatment to evaluate the efficacy of this compound unless there appeared locoregional recurrence and/or distant metastases.

Response criteria

Tumour response was graded as complete response (CR; 100% regression of the tumour and no new lesion), partial response (PR; more than 50% and no new lesion), minor response (MR; more than 25% and not greater than 50% and no new lesion), no change (NC; less than 25% regression and less than 25% progression and no new lesion), progressive disease (PD; not less than 25% progression or new lesion) and not evaluable (NE; either preoperative or postoperative CT was not clear enough to evaluate) evaluated by serial CT scans. Response of MR or better was considered effective. Effective response rate was defined as CR + PR + MR cases divided by overall cases.

Statistical methods

Kaplan–Meyer methods were used for the calculation of survival curves, and a generalised Wilcoxon test was used to assess the statistical significance of survival curves. Fischer's test was used to assess the statistical significance of a survival point. The χ^2 test was used to test significance for bivariate tables.

Results

Patient characteristics

Since the previous report, 1 case in the control group was found to be unsuitable for analysis, as the tumour was a mucin-producing carcinoma, representing a different disease entity from ordinary-type pancreatic cancer. All other cases were confirmed to be ordinary-type pancreatic cancer.

Between July 1999 and March 2002, a total of 81 patients were registered to participate in this trial. Of these, 34 patients were ineligible due to intraoperative findings of peritoneal seeding, liver metastasis or extensive tumours. Ultimately, 47 patients were enrolled in the trial and administered either doranidazole or placebo, and 46 cases were analysed (Fig. 1). Informed consent was obtained from all patients who participated in this trial.

Patient characteristics were as follows. In the doranidazole group (n = 22), male to female ratio was 15:7, and median age was 61.1 years (range 45–74 years). In the control group (n = 24), male to female ratio was 19:5, and median age was 61.3 years (range 50–74 years). No significant differences in background characteristics were noted between

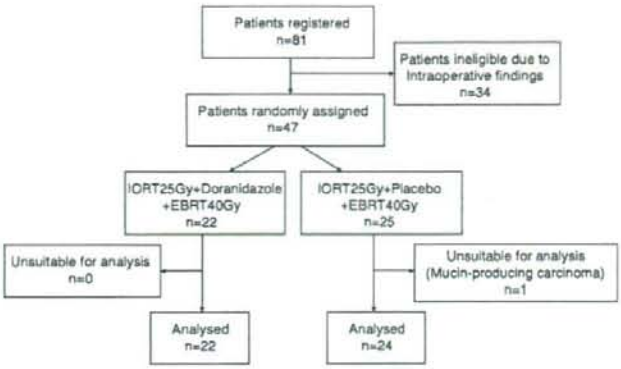

Fig. 1. CONSORT diagram.

groups. Median follow-up period for alive cases was 3.5 years.

Toxicity

As reported previously, the toxicity of doranidazole was not severe and the agent was thus considered safe. Also, there were no severe adverse effects regarding radiation therapy. All patients could receive IORT and EBRT as planned.

Efficacy

As reported previously, the efficacy of IORT with doranidazole for the treatment of pancreatic cancer was evaluated using computed tomography. The committee for evaluating efficacy reported that 9 of 19 patients (47%) in the doranidazole group showed higher effective response rate, compared with 4 of 22 patients (18%) in the control group ($p = 0.043$) (Table 1).

Survival

By the final follow-up in March 2005, all patients from the control group had died of the disease. Survival curves for both trial groups are shown in Fig. 2. Median survival period for the doranidazole group was 318.5 days, compared to 285.5 days for the control group. The 1-year survival rate was 36% ± 10% for the doranidazole and 29% ± 9% for the control group. Although the doranidazole group did not show significantly better survival than the control group, 5 of the 22 doranidazole patients (23%) remained alive >3 years after the trial ended (3-year survival rate: 23% ± 9%), compared with 0 of the 24 patients (3-year survival rate: 0%), in the control group. A significant difference in the 3-year survival rate was thus identified ($p = 0.0192$). As for the 3-year survival rates of the patients in both groups who did not develop distant metastases within 6 months, there was also a significant difference (39% ± 14% in the doranidazole group and 0% in the control group ($p = 0.0169$)).

Table 1
Response of the tumour

	Doranidazole group	Control group
CR	0	0
PR	1	2
MR	8	2
NC	9	15
PD	1	2
NE	0	1
Effective response	47%	18%

Discussion

Pancreatic cancer is known to be exceedingly refractory, and despite considerable effort, 5-year survival results have remained at about 4% for the last 30 years [20]. The standard treatment for locally advanced pancreatic cancer is surgical resection. However, such tumours are often unre-

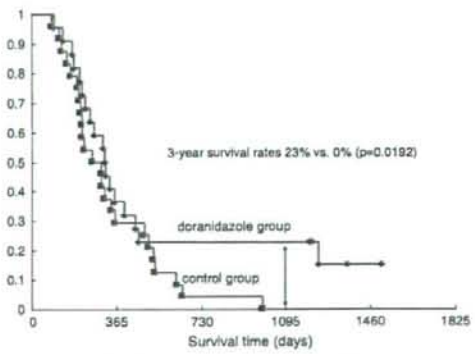

Fig. 2. Survival curves for both groups.

sectable and radiotherapy combined with chemotherapy is then used. With the development of promising new drugs such as gemcitabine [1], prognosis has been slowly improving, and median survival time has reached almost 12 months [5,12,13]. Radiotherapy comprises external beam radiation therapy (EBRT), IORT or a combination of both. IORT, if used by sparing surrounding normal tissue, can be safely combined with EBRT. Despite the technical difficulties, IORT has been used to increase radiation doses to the tumour and reportedly improves long-term survival results [14,15]. Efforts have been made to combine chemotherapy, IORT and EBRT [16].

We reported previously that although long-term survival tended to be better in the doranidazole group, median survival time was the same in both groups [24]. The present study involved a reanalysis of old and additional data, revealing a significant difference in 3-year survival rates. All five patients in the doranidazole group who had been alive at around 2 years or longer on initial analysis had achieved local control, developed no distant metastases and survived a relatively long period of time with local control.

As is often the case with trials involving pancreatic cancer, differences in survival were complicated by the early development of distant metastases even if the trial arm offered theoretically promising intensification of radio- and/or chemotherapy [2,7–9,22]. Obtaining definitive evidence is thus considered difficult in the treatment of pancreatic cancer.

Since this trial was performed in a multicentre double-blinded fashion, any achievement of a significant difference might well be considered attributable to the contribution of this radiosensitiser to the enhancement of IORT dose and thus enhancement of total radiation dose, in turn facilitating local tumour control and eventually improving long-term survival. Although various reports have suggested that escalating total irradiation dose to improve survival has no meaning, our data are among the first few to show that dose escalation can enhance local tumour effects, and thus enhance long-term survival.

The difference in 3-year survival rates was greater for cases in which distant metastases had not developed within 6 months (doranidazole group, 39%; control group, 0%). Survival rates might well be masked by early metastases.

This trial used radiotherapy alone, without chemotherapeutic agents such as 5-fluorouracil or gemcitabine, to evaluate the true efficacy of doranidazole. If a standard chemotherapy regimen was added, short-term survival might be improved due to the prevention of distant metastases. Data might then be comparable to those in curatively resected cases. Given these promising results, a well-designed clinical trial is necessary to optimise the combination of treatments.

Regarding adverse effects, as in the phase I trial, no severe adverse effects have been observed in this phase III trial. Doranidazole is considered quite a safe drug, although only intravenous administration can be performed. This point is quite essential, as numerous radiosensitisers have been abandoned due to inherent toxicities. Future studies need to confirm these promising findings.

Finally, since this drug is a hypoxic cell radiosensitiser, testing of this novel compound may be warranted for other tumours for which hypoxia poses a problem.

Acknowledgements

The authors are grateful to the PR-350 study group: Kumamoto University (Touru Beppu, Ryuiti Nishimura), Kyushu University (Kazuhiro Mizumoto), Kyusyu Medical Center (Michiyasu Nonaka, Satoru Uehara), Kurume University (Masao Hara, Etsuyo Ogo), Yamaguchi University (Kotaro Yamamoto, Yuichi Karino), Kochi Medical College (Michiya Kobayashi, Yasuhiro Ogawa), Shikoku Cancer Center (Minoru Tanada, Masaaki Kataoka), Ehime University (Humiki Kushihata, Takasi Fujii), Kobe University (Yasuyuki Suzuki, Toshinori Soejima), Osaka University (Masato Sakan, Eiichi Tanaka), Osaka City University (Yuji Nishino, Haruyuki Fukuda), Kyoto University (Ryuichirou Doi, Natuo Ooya), Fukui Medical University (Kanji Katayama, Masanori Yoshida), Fukui Red Cross Hospital (Yuki Hirose, Masato Noguchi), Aichi Cancer Center (Kenzo Yasui, Nobukazu Fuwa), Yokohama City University (Yasuhiko Miura, Ichiro Ogino), Toranomon Hospital (Goro Watanabe, Atushi Okazaki), Social Insurance Central General Hospital (Yasutugu Bandai, Kozou Makita), Chiba Cancer Center (Hiroshi Yamamoto, Kazuo Hatano), Saitama Cancer Center (Hirihiko Sakamoto, Mizuyoshi Sakura), Tsukuba University (Takeshi Todoroki, Kiyoshi Ohara), Tochigi Cancer Center (Shoichi Hishinuma, Iwao Tsukishima), Yamagata University (Kouichirou Ozawa, Yasushi Hamamoto) and Hirosaki University (Ken-ichi Hakamada, Masahiko Aoki).

* **Corresponding author. Katsuyuki Karasawa**, Department of Radiology, Tokyo Metropolitan Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. *E-mail address:* karasawa@cick.jp

Received 22 June 2007; received in revised form 9 February 2008; accepted 9 February 2008; Available online 14 March 2008

References

[1] Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 1994;12:29–34.

[2] Ceha HM, van Tienhoven G, Gouma DJ, et al. Feasibility and efficacy of high dose conformal radiotherapy for patients with locally advanced pancreatic carcinoma. Cancer 2000;89:2222–9.

[3] Coleman CN, Buswell L, Noll L, Riese N, Rose MA. The efficacy of pharmacokinetic monitoring and dose modification of etanidazole on the incidence of neurotoxicity: results from a phase II trial of etanidazole and radiation therapy in locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 1992;22:565–8.

[4] Coleman CN. Conference summary: the ninth international conference on the chemical modifiers of cancer treatment. Br J Cancer Suppl 1996;27:S297–304.

[5] Crane CH, Antolak JA, Rosen II, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. Int J Gastrointest Cancer 2001;30:123–32.

[6] Eschwege F, Sancho-Garnier H, Chassagne D, et al. Results of a European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. Int J Radiat Oncol Biol Phys 1997;39:273–4.

[7] Furuse J, Kinoshita T, Kawashima M, et al. Intraoperative and conformal external-beam radiation therapy with protracted

5-fluorouracil infusion in patients with locally advanced pancreatic carcinoma. Cancer 2003;97:1346–52.
[8] Garton GR, Gunderson LL, Nagorney DM, et al. High-dose preoperative external beam and intraoperative irradiation for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 1993;27:1153–7.
[9] Gunderson LL, Nagorney DM, Martenson JA, et al. External beam plus intraoperative irradiation for gastrointestinal cancers. World J Surg 1995;19:191–7.
[10] Kuno Y, Shinomiya N. PR-000350, a novel hypoxic radiosensitizer, enhances tumor cell killing by promoting apoptosis preferentially in the S-phase fraction. Apoptosis 2000;5:69–77.
[11] Lee DJ, Cosmatos D, Marcial VA, et al. Results of an RTOG phase III trial (RTOG 85-27) comparing radiotherapy plus etanidazole with radiotherapy alone for locally advanced head and neck carcinomas. Int J Radiat Oncol Biol Phys 1995;32:883–5.
[12] Li CP, Chao Y, Chi KH, et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 2003;57:98–104.
[13] McGinn CJ, Zalupski MM, Shureiqi I, et al. Phase I trial of radiation dose escalation with concurrent weekly full-dose gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2001;19:4202–8.
[14] Mohiuddin M, Cantor RJ, Biermann W, Weiss SM, Barbot D, Rosato FE. Combined modality treatment of localized unresectable adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys 1988;14:79–84.
[15] Nishimura Y, Hosotani R, Shibamoto Y, et al. External and intraoperative radiotherapy for resectable and unresectable pancreatic cancer: analysis of survival rates and complications. Int J Radiat Oncol Biol Phys 1997;39: 39–49.
[16] Okamoto A, Matsumoto G, Tsuruta K, et al. Intraoperative radiation therapy for pancreatic adenocarcinoma: the Komagome hospital experience. Pancreas 2004;28:296–300.
[17] Overgaard J, Hansen HS, Andersen AP, et al. Misonidazole combined with split-course radiotherapy in the treatment of invasive carcinoma of larynx and pharynx: report from the DAHANCA 2 study. Int J Radiat Oncol Biol Phys 1989;16:1065–8.
[18] Overgaard J. Sensitization of hypoxic tumour cells – clinical experience. Int J Radiat Biol 1989;56:801–11.
[19] Overgaard J, Hansen HS, Overgaard M, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol. 1998;46:135–46.
[20] Rubin P, Williams JP, Okunieff P, et al. Statement of the clinical oncologic problem. In: Rubin P, editor. Clinical oncology: a multidisciplinary approach for physicians and students. Philadelphia: WB Saunders; 2001. p. 1–31.
[21] Shibamoto Y, Kubota T, Kishii K, et al. Radiosensitivity of human pancreatic cancer cells in vitro and in vivo, and the effect of a new hypoxic cell sensitizer, doranidazole. Radiother Oncol 2000;56:265–70.
[22] Shipley WU, Wood WC, Tepper JE, et al. Intraoperative electron beam irradiation for patients with unresectable pancreatic carcinoma. Ann Surg 1984;200:289–96.
[23] Sunamura M, Matsuno S, Okamoto A, et al. Phase I clinical trial for the effect of a radiosensitizer, PR-350 (doranidazole) combined with intraoperative radiation therapy in the treatment of pancreatic carcinoma. Suizo 2003:18–23.
[24] Sunamura M, Karasawa K, Okamoto A, et al. Phase III trial of radiosensitizer PR-350 combined with intraoperative radiotherapy for the treatment of locally advanced pancreatic cancer. Pancreas 2004;28:330–4.

●特 集● 放射線治療の進歩—多分割照射の基礎と臨床—

頭頸部癌に対する過分割照射法の実際

唐澤 克之[*1] 羽生菜穂子[*1] 張 大鎮[*1] 久賀 元兆[*1] 神沼 拓也[*1]
三橋 敏雄[*2] 宮下 久夫[*2]

〔*Jpn J Cancer Chemother* 35(11): 1827-1832, *November*, 2008〕

Hyperfractionated Radiation Therapy for Head and Neck Cancers: Katsuyuki Karasawa[*1], Nahoko Hanyu[*1], Ta-Chen Chang[*1], Gencho Kuga[*1], Takuya Kaminuma[*1], Toshio Mitsuhashi[*2] and Hisao Miyashita[*2] ([*1]*Division of Radiation Oncology*, [*2]*Otorhinolaryngology, Head and Neck Tumor Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital*)

Summary

Among various altered fractionation regimens, hyperfractionated radiotherapy (HFRT) has been considered effective to raise survival rate (SR) as well as local control rate (LCR) in head and neck cancers. We reviewed our results of HFRT (117 cases) treated between 1995 and 2004 and compared with those of conventionally fractionated radiotherapy (CFRT; 80 cases) treated during the same period. By disease site, naso-/oro-/hypopharynx/larynx were 5/23/44/45 vs. 10/6/10/54. There were more advanced-stage cases in HFRT group (stage Ⅰ/Ⅱ/Ⅲ/Ⅳ=19/36/23/35 vs. 42/16/8/14). Median RT dose were 72 Gy vs. 66 Gy. In 71 cases, chemotherapy was added (HF/CF=54/17). In stage Ⅲ and Ⅳ cases, there was a borderline significant difference in LCR (at 5 years; 44.3% for HFRT group vs. 24.5% for CFRT group; p=0.0502), and a tendency in SR (at 5 years; 50.7% for HFRT group vs. 16.7% for CFRT group; p=0.1210). By disease site, LCR of HFRT group was higher in hypopharynx (p=0.0005) and oropharynx (p=0.0003), and SR of HFRT group was higher in hypopharynx (p=0.0023). Acute toxicity was heavy but in most cases it was tolerable and there were no severe late toxicities. From our data, it was suggested that HFRT might be effective in certain kinds of head and neck cancers. **Key words**: Head and neck cancer, Radiotherapy, Hyperfractionated radiotherapy, Hypopharyngeal cancer, Oropharyngeal cancer, Chemoradiotherapy, **Corresponding author**: Katsuyuki Karasawa, Division of Radiation Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

要旨 頭頸部癌に対する1日複数回照射法のなかで1回1.1～1.3 Gyを1日2回照射する過分割照射法は，急性期の有害事象は増すものの局所制御率を改善し，一部疾患においては生存率も改善するとされている。今回当施設において行われている過分割照射法による頭頸部癌の方法と治療成績をreviewした。適応は喉頭癌もしくは咽頭癌で遠隔転移を有さず，過分割照射に耐え得る症例で，Shrinking field techniqueを用いて，GTVに対して1回1.2 Gy，1日2回，総線量72 Gy程度まで(60～80 Gy)腫瘍の反応に応じて投与する。1995～2004年までの10年間に過分割照射を施行された117例(HF群)と，同時期に単純分割照射を施行された80例(CF群)とを比較した。症例の偏りがあり全体としては局所制御率，生存率ともに有意差はなかったが，Ⅲ期，Ⅳ期の症例については5年局所制御率が(44.3% vs 24.5%: p=0.0502)，また5年生存率も(50.7% vs 16.7%: p=0.1210)と有意に良好な傾向を認めた。疾患別には下咽頭癌，中咽頭癌において，局所制御率が向上しており，また下咽頭癌においては生存率でも有意に向上していた。高度な晩期有害事象は認められなかった。過分割照射は特に局所遠行例で局所制御に優れていた。今後は化学療法との併用治療の上で，どのように併用していくかが課題である。

[*1] 東京都立駒込病院・放射線科
[*2] 同 ・耳鼻咽喉科・頭頸部腫瘍科

連絡先: 〒113-8677 東京都文京区本駒込3-18-22 東京都立駒込病院・放射線科
唐澤 克之

0385-0684/08/¥500/論文/JCLS

Ⅰ．背　景

2007年の第31回日本頭頸部癌学会のシンポジウムで，初めて頭頸部癌における多分割照射法がテーマとして取り上げられた。

欧米において1日1回2Gy，週間線量10Gy，総線量60～70Gyの照射法の成績では早期癌も局所進行癌も満足な成績をあげられていなかった。そこで1960年代より，癌細胞および正常細胞の放射線生物学的特徴から，分割回数を1日複数回に増やす一方で，1回線量を低下させることにより，治療可能比の向上をめざすことが始められた。これまで数多くの臨床試験において，局所制御率の改善は認められ，有用性が示唆されてきた[1-3]。2006年のBourhisらの1日複数回照射法のランダム化比較試験を集めたメタアナリシスにより，そのうちの過分割照射法が有意に生存率まで改善していると報告された[4]。

一方，わが国においては健康保険上の制限もあり，一部の施設を除いてあまり積極的に1日複数回照射法は行われてこなかったが，海外からの有望な報告および1996年の健康保険改訂により，複数回の照射が2回まで算定することが可能になったことにも起因して，本治療法が一般に行われるようになった。そのなかでも多くの施設は1回1.2Gy程度の線量を使用した過分割照射法が行われてきている。しかし，多くの施設ではまとまった報告がなされてこなかった現状がある。

本シンポジウムでは多分割照射法の生物学的な原理，メタアナリシスの動向および臨床成績の報告がなされたが，本稿では頭頸部癌に対する1日複数回照射法のうち最も一般的な過分割照射法の実際の方法と，当院におけるこれまでの症例の成績を供覧し，考察する。

Ⅱ．過分割照射の実際

1．適　応

喉頭癌（声門癌T1N0でnon bulkyなものを除く），中咽頭癌，下咽頭癌，上咽頭癌（T1/2N0例を除く）で遠隔転移を有さず，また過分割照射に耐えられる全身状態を有するcaseを対象とする。

2．照射方法

GTV（肉眼的腫瘍体積）は原発巣＋腫大したリンパ節，CTV（臨床的標的体積）は声門癌のT1，T2N0およびⅠ期の中咽頭癌，下咽頭癌を除き，原則として原発巣＋所属リンパ節を含む領域に設定する。原則として照射時には頭頸部固定具を使用する。CTVに5mm程度の位置のずれ（セットアップエラー）を見込んで，PTV（計画標的体積）を設定する。

原発巣＋所属リンパ節を含む領域（鎖骨上リンパ節を含む）に左右対向二門＋前方一門照射で1回線量1.2Gyにて40Gy程度（39.6～40.8Gy）まで投与（図1）する。その時点で照射範囲から脊髄を遮蔽し（図2），以後後頸部は電子線（9MeV）照射に変更する。その照射技法で照射を行い，予防照射領域は50～60Gy程度にて終了する。視神経，脳幹部も50Gyを超えないように注意する（50.4Gyにて終了）。それ以降60Gyからは原発巣および腫大リンパ節に照射範囲を限局させ，同部位には腫瘍の縮小に応じて72Gy程度（66Gyから最大81.6Gy）投与する。放射線源としては4MVもしくは6MVのX線を使用する。

放射線生物学的に1日2回の照射の間には6時間の間隔を空ければよいとされているため，照射の時刻は典型的には勤務時間帯内の9時と15時というようなタイミングで行われる。月曜から金曜までの5日間，週10回照射を施行する。

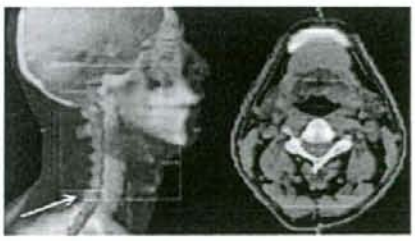

図1　最初の照射野と線量分布の例（中咽頭癌）
後頸部および咽頭周囲のリンパ節も含んで設定する。矢印部鎖骨上リンパ節の照射野とのオーバーラップを防ぐため，10mmほど脊髄を遮蔽する。

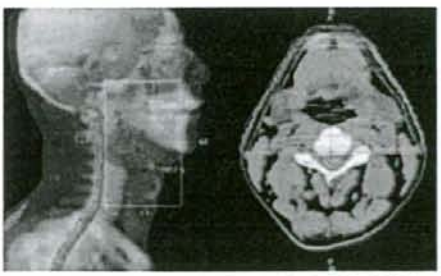

図2　40Gyにて脊髄を遮蔽した後の照射野と線量分布
後頸部のリンパ節には脊髄への距離を考慮に入れ，9MeVの電子線で照射を行う。

3．照射中の全身管理

治療の成否には照射範囲の設定と，照射中の全身管理が最も重要である。主たる急性有害事象である咽頭，口腔粘膜炎の軽減目的に粘膜保護剤もしくは粘膜保護作用のある含嗽剤を使用する。また治療中の栄養管理が重要であるため，鼻腔栄養，TPN，胃管からの栄養など，粘膜炎によって影響を受けない栄養補給法も検討する。さらに患者が高齢の場合には，早めに照射範囲を小さくさせることとともに，誤嚥性肺炎の併発に特に注意する。

表1 患者背景

		HF	CF
症例数	197	117	80
性別			
男性	177	104	73
女性	20	13	7
年齢	34～89	40～88	34～89
中央値	67	65	68
原発部位			
上咽頭	15	5	10
中咽頭	29	23	6
下咽頭	54	44	10
喉頭	99	45	54
Stage			
I	60	18（%）	42（%）
II	61	46（%）	15（%）
III	30	19（%）	11（%）
IV	46	34（%）	12（%）
総線量（Gy）		57.6～81.6	56～76
中央値		72	66
全治療期間（日）		35～65	40～64
中央値		44	46
化学療法の有無			
あり	71	54	17
なし	126	63	63

III．当院における治療成績

1995年1月～2004年12月に根治的な放射線治療を施行した頭頸部扁平上皮癌のうち上咽頭，中咽頭，下咽頭，喉頭癌を対象とした。対象患者は，197例で過分割照射群（HF群）117例，通常分割群（CF群）が80例であった。患者背景を表1，2に示す。後方視的な検討であるため，表2に示すように疾患・病期により治療法の選択に偏りが生じており，CF群では早期喉頭癌が多く，HF群では局所進行癌が多かった。放射線治療はHF群では1回線量は1.2 Gyを使用し，6時間以上の間隔を空けて1日2回の照射を行った。総線量は57.6～81.6 Gyで，基本的には治療終了時にCR-PRになるように治療に対する腫瘍の反応に応じて総線量を決定した。CF群では1回線量は1.8～2.0 Gyを使用した。総線量は56～76 Gyで，HF群と同様に腫瘍の反応により総線量を決定した。総線量はHF群で高く，治療期間は両群に差はなかった。

化学療法が71例で施行され，HF群で化学療法が併用された症例は54例であった。使用されたレジメンは，

表2 患者背景（2）

Stage	HF群				CF群			
	I	II	III	IV	I	II	III	IV
上咽頭	0	1 (1)	1 (1)	3 (2)	1	3 (2)	2 (2)	4 (2)
中咽頭	3 (1)	6 (2)	4 (2)	10 (7)	0	0	3 (2)	3 (2)
下咽頭	6 (2)	11 (5)	9 (6)	18 (13)	2 (2)	0	4 (3)	4 (2)
喉頭	9	28 (8)	5 (3)	3 (1)	39	12	2	1
Total	18 (3)	46 (16)	19(12)	34 (23)	42 (2)	15 (2)	11 (7)	12 (6)

* （ ）内は化学療法施行症例数

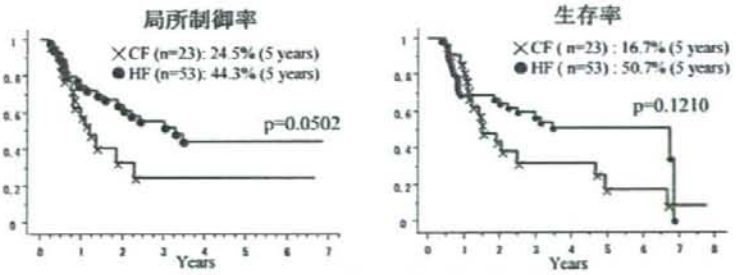

図3 stage III，IV症例の局所制御率と生存率
II期でやや差があるが，有意差は認められなかった。

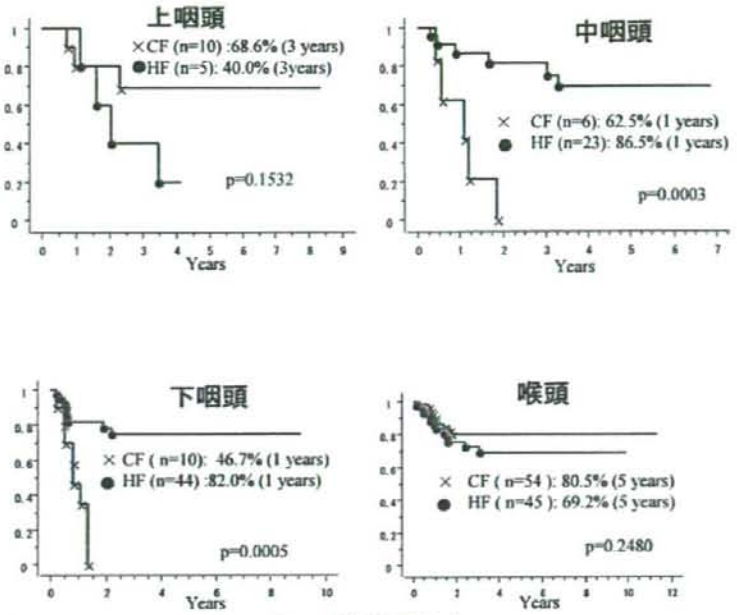

図 4 部位別局所制御率

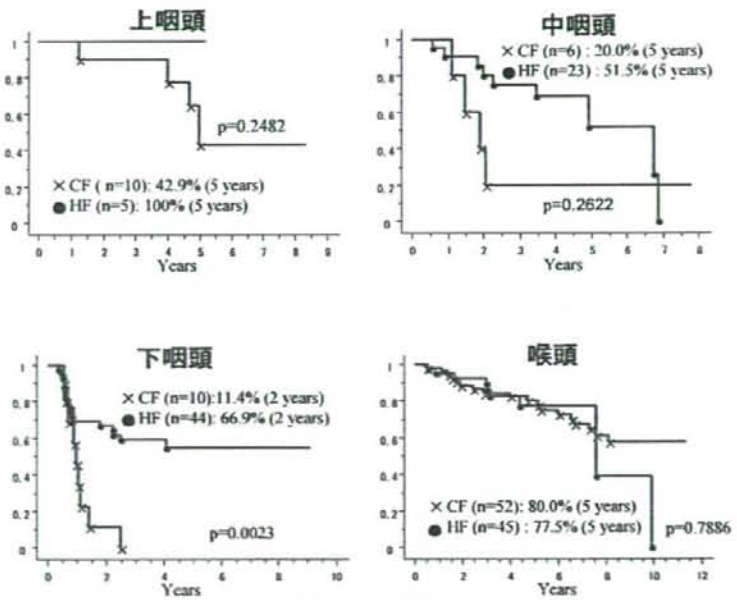

図 5 部位別生存率

導入化学療法・同時併用法としてはプラチナ系を含むものが多く，後治療としてはS-1，UFTの使用が多かった。

全症例の経過観察期間は，0.36～11.3年（中央値3.42年）であった。

5年局所制御率はHF群で67.4%，CF群で66.3%（p=0.6633），5年生存率はHF群で65.3%，CF群で63.0%（p=0.9757）といずれも有意差は認められなかった。早期癌，局所進行期癌の局所制御率・生存率を図3

に示す。統計的な有意差は認められなかったが，進行期癌の特に局所制御率でHF群が良好である傾向があった。部位別の局所制御率を図4，全生存率を図5に示す。下咽頭癌，中咽頭癌では，CF群と比較してHF群で局所制御率が有意に良好で，下咽頭癌では全生存率も有意に良好であった。

局所進行癌の化学療法の併用の有無による局所制御率と生存率は，4年の局所制御率が，CF群で化学療法あり25%，なしが23%（p=0.9433），HF群で化学療法あり44%，なしが43%（p=0.2315）であった。また5年の生存率は，CF群で化学療法あり34%，なしが10%（p=0.5699），HF群で化学療法あり56%，なしが41%（p=0.1215）であった。化学療法の併用による局所制御・生存率の有意な改善は認められなかった。

照射による粘膜炎のため，1週間以上の照射休止を必要とした患者は，HF群で6例（3%），CF群では1例（1%）であり，粘膜炎により麻薬が必要となった患者は，HF群で19例（9.6%），CF群で1例（1%）とHF群で急性期の粘膜炎が強い結果となった。しかし，grade 3以上の晩期の有害事象は認められなかった。また，化学療法を併用することによる急性期および晩期の有害事象の増加は認められなかった。

Ⅳ. 考　察

頭頸部癌治療において放射線治療の役割は非常に大きく，放射線治療が成功した場合には，嚥下・発声・美容面などで患者にもたらされる利益は非常に大きい。この領域における最近の手術技術の進歩，再建技術の進歩，放射線治療計画の技術の進歩に伴い，早期頭頸部癌の治療成績は比較的良好となったと考えられる。しかし局所進行癌では，いまだにその局所制御率・生存率・機能温存率において治療成績は満足がいくものとはいい難く，ここ最近では放射線生物学の概念に基づき，多分割照射法，なかでも過分割照射法において，局所制御率および一部においては生存率までも向上が認められている。

一方，Pignonらのメタアナリシス[5]により，化学療法を放射線療法に併用することにより生存率の向上が認められたことなどから，最近の傾向としては化学放射線療法が局所進行頭頸部癌の標準治療になりつつある。

またBrizelらは過分割照射法に化学療法を併用することで局所制御率をさらに改善させ，化学療法併用の有用性を示唆した[6]。Brizelによれば，過分割照射はすでに通常分割法の化学放射線療法が非常に有害事象が大きく，そこで用いる放射線治療を過分割照射法に代えることによるメリットはそう大きくはないといっている[7]。

しかしながら，化学療法の併用によってもいまだ十分良好な局所制御率，および生存率が得られているとは依然としていえず，さらなる治療成績の改善をめざす価値はあると考えられる。

Bourhisらのメタアナリシス[4]において，過分割照射法は比較的若年層には局所制御率の向上だけでなく生存率の向上も得られ，有用であるとされているが，高齢者には有害事象のためそのメリットが失われる，とされている。

高齢者に対しては，1回線量を通常の1.2 Gyから1.15 Gyもしくは1.1 Gyに低下させたり，N0例に対しては予防的な照射野を広範にとらないようにするという方策が考えられる。

一方で局所制御率を向上させることが必要な腫瘍は，一般的に切除不能で大きい腫瘍が多いため，広い照射野の設定が必要で，また最近は高齢の患者も多いことから，その照射野の設定法には一層の工夫が必要になってくる。

NCCNの診療ガイドライン[8]においては，頭頸部癌に対する多分割照射法は，化学放射線療法の普及もあってⅠ～Ⅱ期の声門癌や早期の中咽頭癌など限られた腫瘍において推奨されているにすぎないが，もう一つのガイドラインであるCancerNetにおいては，まだ研究中の治療として，過分割照射法が数多くの部位に対して，その治療法の選択肢としてあげられている[9]。

また化学療法の有用性を示したBrizelの報告においても試験群の放射線治療は過分割照射法が採用されており[6]，過分割照射法の有用性は局所進行咽頭喉頭癌において，さらに検討されるべき治療法であると考えられる。

もちろんその際には腫瘍の反応から患者の全身管理に至るまで，詳細な患者の観察が必要である。そのために耳鼻科と放射線科の間の密接な連携が極めて重要であることはいうまでもない。

また今後局所進行癌においては，いかに最適な化学療法の併用法を検討することと，さらに最近開発が著しい分子標的薬などとの併用方法についても検討が必要である[10]。

結　論

過分割照射法について，その実際と当院における治療成績を検討した。局所進行頭頸部癌の標準治療は化学放射線療法に移行しつつあるが，局所の制御は患者の社会生活にも重要な影響を与えるものであるため，いまだ十分とはいえない成績向上のためには，過分割照射法は有用な方法の一つである。部位的には下咽頭癌，中咽頭癌が有望である。