Madison, WI) according to the manufacture's instructions and radio-labeled with [^{35}S]-methionine (PerkinElmer, Waltham, MA).

Caspase cleavage assays

For *in vitro* caspase cleavage assay, *in vitro* translated hScrib labeled with [^{35}S] methione was incubated in the presence of recombinant caspase-3 (Chemicon, Temecula, CA), caspase-6 (Alexis, Lausen, Switzerland), caspase-7 (Chemicon) or Caspase-8 (BioVision, San Francisco, CA) at 37 °C for 1 h. The reaction was terminated by the addition of SDS loading buffer and boiling. The reaction mixtures were analyzed by SDS-PAGE and autoradiography.

Plasmids

For *in vitro* expression, the cDNA for Scrib was subcloned into the BamHI/NotI sites of pCDNA3. The Scrib Ala substitution mutants of Asp were constructed using overlap polymerase chain reaction (PCR) with Scrib cDNA as a template using the following primers:

5′-CCTTGCCAGCCA**GCC**TCTGGGTCGCCC-3′ (Asp504Ala)

5′-GGCCTGAGTGAA**GCC**TCTCGCCCATCTGCC-3′ (Asp526Ala)

5′-GTGAACGGGCAA**GCC**GTGCGGGATGCC-3′ (Asp_{1068}Ala)

5′-CAAGACGTGCGG**GCT**GCCACGCACCAAG-3′ (Asp_{1071}Ala)

5′-GGCAACCCCCGC**GCC**CCCACAGACGAG-3′ (Asp_{1131}Ala)

5′-CGCGACCCCACA**GCC**GAGGGCATCTTC-3′ (Asp_{1134}Ala)

To generate the deletion mutants of hScrib, the following cDNA sequences were amplified with polymerase chain reaction (PCR) and subcloned into pCDNA3: LRR + PDZ 1–3 (amino acids 1–1096); LRR + PDZ 1–2 (amino acids 1–953); LRR + PDZ 1a (amino acids 1–819); LRR + PDZ 1b LRR + LAPSDb (amino acids 1–495).

For GFP fusions wild type and mutant *human scribble* cDNA were cloned into the HindIII/EcoRI sites of pEGFP–C1 vector.

TUNEL assay

Human HaCaT cells were grown overnight on cover slips before induction of apoptosis.

After induction of apoptosis, cells were washed with PBS and fixed with 3.7% paraformaldehyde in PBS for 30 min, followed by permeabilization with 0.2% (v/v) Triton X-100 in PBS for 5 min.

The TUNEL assay was carried out using Promega Dead-END™ Fluorometric TUNEL System (Promega) according to the manufacture's instructions.

Acknowledgements

This work was supported by the Grant from the Mitsui Life Social Welfare Foundation (to S. N.) and the Grant-in-aid number 16591645 (to S. N.) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

Albertson, R., Chabu, C., Sheehan, A. & Doe, C.Q. (2004) Scribble protein domain mapping reveals a multistep localization mechanism and domains necessary for establishing cortical polarity. *J. Cell Sci.* **117**, 6061–6070.

Audebert, S., Navarro, C., Nourry, C., Chasserot-Golaz, S., Lecine, P., Bellaiche, Y., Dupont, J.L., Premont, R.T., Sempere, C., Strub, J.M., Van Dorsselaer, A., Vitale, N. & Borg, J.P. (2004) Mammalian Scribble forms a tight complex with the βPIX exchange factor. *Curr. Biol.* **14**, 987–995.

Bilder, D. (2003) PDZ domain polarity complexes. *Curr. Biol.* **13**, R.661–R.662.

Bilder, D. (2004) Epithelial polarity and proliferation control: links from the *Drosophila* neoplastic tumor suppressors. *Genes Dev.* **18**, 1909–1925.

Bilder, D. & Perrimon, N. (2000) Localization of apical epithelial determinants by the basolateral PDZ protein Scribble. *Nature* **403**, 676–680.

Bilder, D., Birnbaum, D., Borg, J.P., Bryant, P., Huigbretse, J., Jansen, E., Kennedy, M.B., Labouesse, M., Legouis, R., Mechler, B., Perrimon, N., Petit, M. & Sinha, P. (2000) Collective nomenclature for LAP proteins. *Nat. Cell Biol.* **2**, E114.

Bojarski, C., Weiske, J., Schoneberg, T., Schroder, W., Mankertz, J., Schulzke, J.D., Florian, P., Fromm, M., Tauber, R. & Huber, O. (2004) The specific fates of tight junction proteins in apoptotic epithelial cells. *J. Cell Sci.* **117**, 2097–2107.

Brancolini, C., Lazarevic, D., Rodriguez, J. & Schneider, C. (1997) Dismantling cell–cell contacts during apoptosis is coupled to a caspase-dependent proteolytic cleavage of f-catenin. *J. Cell Sci.* **139**, 759–771.

Brumby, A.M. & Richardson, H.E. (2003) scribble mutants cooperate with oncogenic Ras or Notch to cause neoplastic overgrowth in *Drosophila*. *EMBO J.* **22**, 5769–5779.

Dow, L.E., Brumby, A.M., Muratore, R., Coombe, M.L., Sedelies, K.A., Trapani, J.A., Russell, S.M., Richardson, H.E. & Humbert, P.O. (2003) hScrib is a functional homologue of the *Drosophila* tumour suppressor Scribble. *Oncogene* **22**, 9225–9230.

Dow, L.E., Kauffman, J.S., Caddy, J., Zarbalis, K., Peterson, A.S., Jane, S.M., Russell, S.M. & Humbert, P.O. (2007) The tumour-suppressor Scribble dictates cell polarity during directed epithelial migration: regulation of Rho GTPase recruitment to the leading edge. *Oncogene* **26**, 2272–2282.

Gardiol, D., Kuhne, C., Glaunsinger, B., Lee, S.S., Javier, R. & Banks, L. (1999) Oncogenic human papillomavirus E6 proteins target the discs large tumour suppressor for proteasome-mediated degradation. *Oncogene* **18**, 5487–5496.

Gardiol, D., Zacchi, A., Petrera, F., Stanta, G. & Banks, L. (2006) Human discs large and scrib are localized at the same regions in colon mucosa and changes in their expression patterns are

correlated with loss of tissue architecture during malignant progression. *Int. J. Cancer* **119**, 1285–1290.

Gregorc, U., Ivanova, S., Thomas, M., Guccione, E., Glaunsinger, B., Javier, R., Turk, V., Banks, L. & Turk, B. (2007) Cleavage of MAGI-1, a tight junction PDZ protein, by caspases is an important step for cell–cell detachment in apoptosis. *Apoptosis* **12**, 343–354.

Gregorc, U., Ivanova, S., Thomas, M., Turk, V., Banks, L. & Turk, B. (2005) hDLG/SAP97, a member of the MAGUK protein family, is a novel caspase target during cell–cell detachment in apoptosis. *Biol. Chem.* **386**, 705–710.

Hariharan, I.K. & Bilder, D. (2006) Regulation of imaginal disc growth by tumor-suppressor genes in *Drosophila*. *Annu. Rev. Genet.* **40**, 335–361.

Humbert, P., Russell, S. & Richardson, H. (2003) Dlg, Scribble and Lgl in cell polarity, cell proliferation and cancer. *Bioessays* **25**, 542–553.

Igney, F.H. & Krammer, P.H. (2002) Death and anti-death: tumour resistance to apoptosis. *Nat. Rev. Cancer* **2**, 277–288.

Ivanova, S., Repnik, U., Banks, L., Turk, V. & Turk, B. (2007) Cellular localization of MAGI-1 caspase cleavage products and their role in apoptosis. *Biol. Chem.* **388**, 1195–1198.

Jacobson, M.D., Weil, M. & Raff, M.C. (1997) Programmed cell death in animal development. *Cell* **88**, 347–354.

Janicke, R.U., Ng, P., Sprengart, M.L. & Porter, A.G. (1998) Caspase-3 is required for α-fodrin cleavage but dispensable for cleavage of other death substrates in apoptosis. *J. Biol. Chem.* **273**, 15540–15545.

Kucharczak, J., Simmons, M.J., Fan, Y. & Gelinas, C. (2003) To be, or not to be: NF-κB is the answer—role of Rel/NF-κB in the regulation of apoptosis. *Oncogene* **22**, 8961–8982.

Levkau, B., Herren, B., Koyama, H., Ross, R. & Raines, E.W. (1998) Caspase-mediated cleavage of focal adhesion kinase pp125FAK and disassembly of focal adhesions in human endothelial cell apoptosis. *J. Exp. Med.* **187**, 579–586.

Metais, J.Y., Navarro, C., Santoni, M.J., Audebert, S. & Borg, J.P. (2005) hScrib interacts with ZO-2 at the cell–cell junctions of epithelial cells. *FEBS Lett.* **579**, 3725–3730.

Nagasaka, K., Nakagawa, S., Yano, T., Takizawa, S., Matsumoto, Y., Tsuruga, T., Nakagawa, K., Minaguchi, T., Oda, K., Hiraike-Wada, O., Ooishi, H., Yasugi, T. & Taketani, Y. (2006) Human homolog of *Drosophila* tumor suppressor Scribble negatively regulates cell-cycle progression from G1 to S phase by localizing at the basolateral membrane in epithelial cells. *Cancer Sci.* **97**, 1217–1225.

Nakagawa, S. & Huibregtse, J.M. (2000) Human scribble (Vartul) is targeted for ubiquitin-mediated degradation by the high-risk papillomavirus E6 proteins and the E6AP ubiquitin-protein ligase. *Mol. Cell. Biol.* **20**, 8244–8253.

Nakagawa, S., Yano, T., Nakagawa, K., Takizawa, S., Suzuki, Y., Yasugi, T., Huibregtse, J.M. & Taketani, Y. (2004) Analysis of the expression and localisation of a LAP protein, human scribble, in the normal and neoplastic epithelium of uterine cervix. *Br. J. Cancer* **90**, 194–199.

Navarro, C., Nola, S., Audebert, S., Santoni, M.J., Arsanto, J.P., Ginestier, C., Marchetto, S., Jacquemier, J., Isnardon, D., Le Bivic, A., Birnbaum, D. & Borg, J.P. (2005) Junctional recruitment of mammalian Scribble relies on E-cadherin engagement. *Oncogene* **24**, 4330–4339.

Nicholson, D.W. & Thornberry, N.A. (1997) Caspases: killer proteases. *Trends. Biochem. Sci.* **22**, 299–306.

Osmani, N., Vitale, N., Borg, J.P. & Etienne-Manneville, S. (2006) Scrib controls Cdc42 localization and activity to promote cell polarization during astrocyte migration. *Curr. Biol.* **16**, 2395–2405.

Pagliarini, R.A. & Xu, T. (2003) A genetic screen in *Drosophila* for metastatic behavior. *Science* **302**, 1227–1231.

Perez, D. & White, E. (2000) TNF-α signals apoptosis through a bid-dependent conformational change in Bax that is inhibited by E1B 19K. *Mol. Cell* **6**, 53–63.

Petit, M.M., Crombez, K.R., Vervenne, H.B., Weyns, N. & Van de Ven, W.J. (2005a) The tumor suppressor Scrib selectively interacts with specific members of the zyxin family of proteins. *FEBS lett.* **579**, 5061–5068.

Petit, M.M., Meulemans, S.M., Alen, P., Ayoubi, T.A., Jansen, E. & Van de Ven, W.J. (2005b) The tumor suppressor Scrib interacts with the zyxin-related protein LPP, which shuttles between cell adhesion sites and the nucleus. *BMC Cell Biol.* **6**, 1.

Rosenblatt, J., Raff, M.C. & Cramer, L.P. (2001) An epithelial cell destined for apoptosis signals its neighbors to extrude it by an actin- and myosin-dependent mechanism. *Curr. Biol.* **11**, 1847–1857.

Rudel, T. & Bokoch, G.M. (1997) Membrane and morphological changes in apoptotic cells regulated by caspase-mediated activation of PAK2. *Science* **276**, 1571–1574.

Salvesen, G.S. & Dixit, V.M. (1997) Caspases: intracellular signaling by proteolysis. *Cell* **91**, 443–446.

Samejima, K., Svingen, P.A., Basi, G.S., Kottke, T., Mesner, P.W. Jr., Stewart, L., Durrieu, F., Poirier, G.G., Alnemri, E.S., Champoux, J.J., Kaufmann, S.H. & Earnshaw, W.C. (1999) Caspase-mediated cleavage of DNA topoisomerase I at unconventional sites during apoptosis. *J. Biol. Chem.* **274**, 4335–4340.

Santoni, M.J., Pontarotti, P., Birnbaum, D. & Borg, J.P. (2002) The LAP family: a phylogenetic point of view. *Trends Genet.* **18**, 494–497.

Song, Z. & Steller, H. (1999) Death by design: mechanism and control of apoptosis. *Trends Cell Biol.* **9**, M49–M52.

Steinhusen, U., Badock, V., Bauer, A., Behrens, J., Wittman-Liebold, B., Dorken, B. & Bommert, K. (2000) Apoptosis-induced cleavage of beta-catenin by caspase-3 results in proteolytic fragments with reduced transactivation potential. *J. Biol. Chem.* **275**, 16345–16353.

Steinhusen, U., Weiske, J., Badock, V., Tauber, R., Bommert, K. & Huber, O. (2001) Cleavage and shedding of E-cadherin after induction of apoptosis. *J. Biol. Chem.* **276**, 4972–4980.

Steller, H. (1995) Mechanisms and genes of cellular suicide. *Science* **267**, 1445–1449.

Takizawa, S., Nagasaka, K., Nakagawa, S., Yano, T., Nakagawa, K., Yasugi, T., Takeuchi, T., Kanda, T., Huibregtse, J.M., Akiyama, T. & Taketani, Y. (2006) Human scribble, a novel tumor suppressor identified as a target of high-risk HPV E6 for ubiquitin-mediated degradation, interacts with adenomatous polyposis coli. *Genes Cells* **11**, 453–464.

Talanian, R.V., Quinlan, C., Trautz, S., Hackett, M.C., Mankovich,

J.A., Banach, D., Ghayur, T., Brady, K.D. & Wong, W.W. (1997) Substrate specificities of caspase family proteases. *J. Biol. Chem.* **272**, 9677–9682.

Tapon, N. (2003) Modeling transformation and metastasis in *Drosophila*. *Cancer Cell* **4**, 333–335.

Thompson, C.B. (1995) Apoptosis in the pathogenesis and treatment of disease. *Science* **267**, 1456–1462.

Wen, L.P., Fahrni, J.A., Troie, S., Guan, J.L., Orth, K. & Rosen, G.D. (1997) Cleavage of focal adhesion kinase by caspases during apoptosis. *J. Biol. Chem.* **272**, 26056–26061.

Zeitler, J., Hsu, C.P., Dionne, H. & Bilder, D. (2004) Domains controlling cell polarity and proliferation in the *Drosophila* tumor suppressor Scribble. *J. Cell Biol.* **167**, 1137–1146.

Received: 24 November 2007
Accepted: 13 April 2008

ELSEVIER

Auris Nasus Larynx 36 (2009) 310–313

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

www.elsevier.com/locate/anl

Oral pilocarpine (5 mg t.i.d.) used for xerostomia causes adverse effects in Japanese

Naoki Nakamura [a,*], Nakashi Sasano [a], Hideomi Yamashita [a], Hiroshi Igaki [a], Kenshiro Shiraishi [a], Atsuro Terahara [a], Takahiro Asakage [b], Kazunari Nakao [b], Yasuhiro Ebihara [b], Kuni Ohtomo [a], Keiichi Nakagawa [a]

[a] *Department of Radiology, Tokyo University Hospital, Tokyo, Japan*
[b] *Department of Otolaryngology, Tokyo University Hospital, Tokyo, Japan*

Received 23 December 2007; accepted 14 April 2008
Available online 16 July 2008

Abstract

Objective: To evaluate Japanese tolerability to pilocarpine of 5 mg t.i.d.
Methods: From January 2006 to July 2006, 39 patients with xerostomia received 5 mg t.i.d. pilocarpine for at least for 12 weeks unless they had experienced unacceptable adverse effects. All patients received radiotherapy that included the parotid glands in the radiation field >50 Gy. The body weights of the patients ranged from 42 to 73 kg (median 60 kg).
Results: Thirty-six of the 39 patients were evaluable. The tolerated rate was only 47%. Of the 25 patients whose body weights were less than 65 kg, the tolerated rate was 36%, whereas the rate of the 11 patients whose body weights were 65 kg or above was 72% ($p = 0.050$). The most common adverse effect was sweating with an incidence of 64%. Response rate, which was defined as the total number of patients with an increase of at least 25 mm from the baseline in the VAS score divided by the number of maintaining patients among those who started pilocarpine after more than 4 months from the start of radiotherapy, was 40% at 12 weeks ($n = 15$).
Conclusion: For Japanese, 5 mg t.i.d. pilocarpine caused a high incidence of unacceptable adverse effects. A lower dose of pilocarpine needs to be considered.

Keywords: Pilocarpine; Xerostomia; Japanese; Tolerability; Sweating; Radiotherapy

1. Introduction

Lifelong xerostomia associated with salivary dysfunction is a most unpleasant adverse effect resulting from high dose irradiation delivered to the head and neck region [1–5]. Patients with xerostomia experience significant oral discomfort and difficulties in speaking, swallowing, and sleeping [6–9]. These conditions can lead to severe oral disease, nutritional deficiencies and marked decline in quality of life [10].

Treatment of xerostomia is difficult, and previous treatments have included saliva substitutes, hard candy, antimicrobial rinses, and fluoride treatments, all of which have generally been inadequate. Pilocarpine hydrochloride, however, has been approved for effective treatment of radiation-induced xerostomia in many countries. It is a naturally occurring alkaloid that has a broad range of pharmacologic effects, including increasing secretion from the exocrine glands (sweat, salivary, lacrimal, gastric, pancreatic, and intestinal glands). The clinical efficacy of 5–10 mg pilocarpine three times per day (t.i.d.) daily to reduce the symptoms of xerostomia has been studied in several trials in the Western countries [8–18].

On the other hand, pilocarpine is known to cause various kinds of adverse effects expected for a cholinergic agonist (e.g., sweating, rhinitis, nausea, urinary frequency)

* Corresponding author at: Department of Radiology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: +81 3 5880 8667; fax: +81 3 5880 8935.
E-mail address: nnakamur-tky@umin.ac.jp (N. Nakamura).

0385-8146/$ – see front matter
doi:10.1016/j.anl.2008.04.008

[8,11,12]. The severity of these adverse effects is thought to be dose related. According to Rieke et al. pilocarpine's adverse effects were considered acceptable by patients taking 5 mg t.i.d. [11].

Pilocarpine has been available for clinical use from October 2005 in Japan. However, a study has not yet been conducted to determine if 5 mg t.i.d. is the best dose of pilocarpine for Japanese who probably have a different body mass index than Westerners. The purpose of this study was to evaluate the tolerability of Japanese to 5 mg oral pilocarpine t.i.d. daily during or after radiotherapy in head and neck cancer.

2. Materials and methods

2.1. Patients

Thirty-nine patients, who had been suffering from radiation-induced xerostomia, received pilocarpine during or after radiotherapy in our institute. They started to receive pilocarpine between January 2006 and July 2006. All of the patients had head and neck carcinomas and received >50 Gy radiotherapy that included the parotid glands in the radiation field.

The patients' characteristics are summarized in Table 1. Thirty-nine patients consisted of 35 males and 4 females with a median age 61 years. The body weights of the patients ranged from 42 to 73 kg (median 60 kg). Twenty-eight (72%) patients had pharyngeal cancer. Five (13%) patients had laryngeal cancer, three (8%) had oral cancer, two (5%) had unknown primary cancer, and one (3%) had paranasal cavity cancer.

Twenty-three (59%) patients received definitive radiotherapy, while 16 (41%) patients received post-operative radiotherapy. Twenty (51%) patients received concurrent chemotherapy. The prescribed irradiation dose ranged from 60 to 72 Gy (median 70 Gy). The mean dose to both salivary glands ranged from 19.9 to 57.3 Gy (median 41.1 Gy).

Table 1
Patients' characteristics

Characteristics	$n = 39$
Age, years (median)	39–84 (61)
Gender (%)	
Female	10
Male	90
Body weights (%)	
<65 kg	67
>65 kg or =65 kg	33
Tumor site (%)	
Pharynx	72
Epipharynx	15
Mesopharynx	15
Hypopharynx	31
Larynx	13
Oral cavity	8
Primary unknown	5
Paranasal cavity	3
Intent of radiotherapy (%)	
Definitive radiotherapy	59
Post-operative radiotherapy	41
Prescription dose, Gy (median)	60–72 (70)
Mean dose of both salivary glands, Gy (median)	19.9–57.3 (41.1)
Concurrent chemotherapy (%)	
Yes	51
No	49
Duration from the beginning of radiotherapy to the beginning of pilocarpine (%)	
<120 or =120 days	15
>120 days	85

n = number of patients.

2.2. Pilocarpine

All patients received a daily dose of pilocarpine of 5 mg t.i.d. They were seen prior to initiation of treatment and at 2-week intervals thereafter, and continued to receive pilocarpine for at least 12 weeks whether effective or not unless they had experienced unacceptable adverse effects.

The duration from the beginning of radiotherapy to the start of pilocarpine ranged from 2 weeks to 72 months (median 8 months). Thirty-three (85%) patients started pilocarpine 4 months or later from the start of radiotherapy.

2.3. Study outcomes

The primary outcomes were determined by the rate that pilocarpine was maintained for 12 weeks, with or without any adverse effects (defined as tolerated rate). Secondary outcomes included the incidence of adverse effects, and the subjective symptoms of xerostomia.

Adverse effects were reported by telephone as they occurred, or at the bi-weekly appointments throughout the study.

The subjective assessment of efficacy was undertaken through the use of visual analog scales (VAS) every 4 weeks. The 100 mm visual analog scale (VAS) was used to record the response. Patients were asked to rate their condition of the dryness of the mouth on a scale from 0 to 100. This questionnaire was completed before starting pilocarpine for a period of 12 weeks. A patient with an increase of at least 25 mm from the baseline in the VAS score was defined as a "Responder." Response rate was defined as the total number of "Responder" divided by the number of maintaining patients. Response rate, in addition, was calculated among the 30 patients who started pilocarpine after more than 4 months from the start of radiotherapy and were considered to have fixed symptoms of xerostomia.

3. Results

Three of the 39 patients were excluded from the analysis because they stopped taking pilocarpine within 12 weeks for

Table 2
Tolerability of pilocarpine with 5 mg t.i.d.

Status	n	%
Tolerable without any adverse effects	6	17
Tolerable with some adverse effects	11	30
Unacceptable adverse effects	19	53

n = number of patients.

reasons other than adverse effects. (Two of them refused to continue because of insufficient efficacy, and one stopped because of beginning other medication which should not be used concurrently with pilocarpine.).

3.1. Tolerability

Of the remaining 36 patients, the tolerated rate was as low as 47%. Only 17 of the 36 patients were able to continue pilocarpine for 12 weeks with or without any adverse effects. Nineteen (53%) stopped taking pilocarpine within 12 weeks because of unacceptable adverse effects (Table 2).

The duration from the beginning to stopping pilocarpine due to adverse effects ranged from 3 to 42 days (median 7 days).

When we divide patients in less or more than 65 kg, the tolerated rates between two groups showed a significantly difference. Of the 25 patients whose body weights were less than 65 kg, the tolerated rate was 36%, whereas the tolerated rate of the 11 patients whose body weights were 65 kg or more was 72% ($p = 0.050$, calculated by a χ^2-test) (Table 3).

3.2. Incidence of adverse effects

The most common adverse effect was sweating, and its incidence was 64%. Other adverse effects reported included nausea, rhinitis, headache, cervical pain, fatigue, dazzling, oversalivation, and paresthesia of the tongue (Table 4).

Table 3
Tolerated rate according to the patients' body weights

Body weights	n	Tolerated rate (%)
<65 kg	25	36
>65 kg or =65 kg	11	72

n = number of patients; $p = 0.050$.

Table 4
Incidence of adverse effects with a probable relationship to pilocarpine

Adverse effects	% (n = 36)
Sweating	64
Nausea	8
Rhinitis	6
Headache	3
Cervical pain	3
Fatigue	3
Dazzling	3
Oversalivation	3

n = number of patients.

Table 5
Response rate

	Pretreatment	4 weeks	8 weeks	12 weeks
n	30	20	15	15
Response rate (%)	–	10	27	40

n = number of patients.

With the exception of paresthesia of the tongue, all of the other adverse effects which caused patients to quit taking pilocarpine disappeared within 1 week of stopping and were probably related to pilocarpine.

3.3. Subjective symptoms of xerostomia

Response rates at 4, 8, and 12 weeks were 10, 27, and 40%, respectively (Table 5).

4. Discussion

The most common adverse effect of pilocarpine is sweating, and its incidence is thought to be dose related. In the review of two prospective randomized trials that included 369 patients, Rieke et al. reported that the incidence of sweating with pilocarpine was 29% with 5 mg t.i.d, while it was 68% with 10 mg t.i.d. [11] They concluded that the adverse effects were considered acceptable by patients taking 5 mg t.i.d. They also reported that an improvement in dryness was obtained in 51% of patients receiving 5 mg t.i.d. pilocarpine, which was equally effective as 10 mg t.i.d, but 2.5 mg t.i.d was judged to be an ineffective dose.

Our investigation indicated that the incidence of sweating was 62%, and the tolerability was very low in spite of using 5 mg t.i.d. Conceivably, the physical difference between the Japanese and Westerners may explain the discrepancy between our results and those reported by Rieke et al. [11].

In our study, the tolerated rate in patients whose body weights were less than 65 kg was much lower than that in patients whose weights were 65 kg or above ($p = 0.050$). For Japanese patients, especially for those weighting 65 kg or less, 5 mg t.i.d. of pilocarpine appears to be an over dose. The proper dose of pilocarpine may be a little lower than 5 mg t.i.d. for the average Japanese, and perhaps the tolerability can be raised without decreasing efficacy when using a proper dose.

In conclusion, an oral pilocarpine dose of 5 mg t.i.d. caused a high incidence of unacceptable adverse effects for Japanese. A lower dose of pilocarpine needs to be considered in conjunction with body weights to find a proper dose.

References

[1] Eneroth CM, Henrikson CO, Jakobsson P. Effect of fractionated radiotherapy on salivary gland function. Cancer 1972;30:1147–53.

[2] Shannon IL, Starcke EN, Wescott WB. Effect of radiotherapy on whole saliva flow. J Dent Res 1977;56:693.
[3] Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. Eur J Cancer 1992;28:457–62.
[4] Funegerd U, Franzen L, Ericson T, Henriksson R. Parotid saliva composition during and after irradiation of head and neck cancer. Eur J Cancer B Oral Oncol 1994;30B:230–3.
[5] Stephens LC, Ang KK, Schultheiss TE, King GK, Brock WA, Peters LJ. Target cell mode of radiation injury in rhesus salivary glands. Radiother Oncol 1986;7:165–74.
[6] Baum B, Bodner L, Fox PC, Izutsu KT, Pizzo PA, Wright WE. Therapy-induced dysfunction of salivary glands: implications for oral health. Spec Care Dentist 1985;5:274–7.
[7] Mason DK, Glen AIM. The aetiology of xerostomia (dry mouth). Dent Mag Oral Topics 1967;84:235–8.
[8] Leveque FG, Montgomery M, Potter D, Zimmer MB, Rieke JW, Steiger BW, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. J Clin Oncol 1993;11:1124–31.
[9] Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69:751–60.
[10] Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, et al. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. N Engl J Med 1993;329:390–5.
[11] Rieke JW, Hafermann MD, Johnson JT, Leveque FG, Iwamoto R, Steiger BW, et al. Oral pilocarpine for radiation-induced xerostomia: integrated efficacy and safety results from two randomized clinical trials. Int J Radiat Oncol Biol Phys 1995;31:661–9.
[12] Horiot JC, Lipinski F, Schraub S, Maulard-Durdux C, Bensadoum RJ, Ardiet JM, et al. Post-radiation severe xerostomia relieved by pilocarpine: a prospective French cooperative study. Radiother Oncol 2000;55:233–9.
[13] Warde P, O'Sullivan B, Aslanidis J, Kroll B, Lockwood G, Waldron J, et al. A phase three placebo-controlled trial of oral pilocarpine in patients undergoing radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2002;54:9–13.
[14] Niedermeier W, Matthaeus C, Meyer C, Staar S, Muller RP, Schulze HJ. Radiation-induced hyposalivation and its treatment with oral pilocarpine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:541–9.
[15] Gornitsky M, Shenouda G, Sultanem K, Katz H, Hier M, Black M, et al. Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:45–52.
[16] Zimmereman RP, Mark RJ, Tran LM, Juillard GF. Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. Int J Radiat Oncol Biol Phys 1997;37:571–5.
[17] Rode M, Smid L, Budihna M, Soba E, Rode M, Gaspersic D. The effect of pilocarpine and biperiden of salivary secretion during and after radiotherapy in head and neck cancer patients. Int J Radiat Oncol Biol Phys 1999;45:373–8.
[18] Fisher J, Scott C, Scarantino CW, Leveque FG, White RL, Rotman M, et al. Phase three quality-of-life study results: impact of patients' quality of life to reducing xerostomia after radiotherapy for head-and neck cancer RTOG 97-09. Int J Radiat Oncol Biol Phys 2003;56:832–6.

Oral Oncology (2009) 45, e19–e23

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/oraloncology

ORAL ONCOLOGY

Umami taste dysfunction in patients receiving radiotherapy for head and neck cancer

Hideomi Yamashita [a,*], Keiichi Nakagawa [a], Yoshio Hosoi [b], Azusa Kurokawa [c], Yusuke Fukuda [c], Ichiro Matsumoto [c], Takumi Misaka [c], Keiko Abe [c]

[a] *Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyou-ku, Tokyo 113-8655, Japan*
[b] *Section of Radiation Biology, Center for Disease Biology and Integrative Medicine, Faculty of Medicine, University of Tokyo, Tokyo, Japan*
[c] *Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, University of Tokyo, Tokyo, Japan*

Received 17 March 2008; received in revised form 29 March 2008; accepted 1 April 2008
Available online 11 July 2008

KEYWORDS
Umami taste;
Taste loss;
Radiotherapy;
Head and neck cancer;
Whole-mouth taste method

Summary Taste loss is a major cause of morbidity in patients undergoing head and neck irradiation. Previous studies have reported the alteration of the four basic tastes in patients with head and neck cancer during radiotherapy. However, only a few studies have been conducted on the effects of irradiation on the function of *umami* taste, a novel and basic taste recently recognized. In a prospective study, 52 patients undergoing radical head and neck irradiation were assessed for taste loss. Taste ability was measured by the taste threshold for *umami* quality using the whole-mouth taste method in patients before, during, and immediately after radiotherapy. *Umami* taste declined of the 3rd week after the start of radiotherapy and improved of the 8th week.

Introduction

Taste dysfunction is one of the most frequent complaints of patients undergoing radiation therapy (RT) for head and neck cancer. Complaints of taste disorders have been reported in 75% of patients with head and neck cancer undergoing radiation, and 93% of these patients complain of long-term xerostomia.[1] Many patients undergoing dose-intensive radiation experience reduced taste (ageusia) or altered taste (dysgeusia), which may have a significant impact on quality of life (QOL). Patients with taste disturbance experienced greater weight loss than those who did not report a change in taste.[2] On the other hand, patients with taste loss had a worse outcome than those did not lose their sense of taste and were able to maintain their food intake and nutritional support.[3] To design a diet that maximizes

* Corresponding author. Tel.: +81 3 5800 8667; fax: +81 3 5800 8935.
E-mail address: yamashitah-rad@h.u-tokyo.ac.jp (H. Yamashita).

1368-8375/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.oraloncology.2008.04.001

on the remaining taste abilities might result in the most palatable diet to the patients with taste loss and thus, better outcome and QOL might be expected. This would require individual diet management and especially, depend on a well understanding of the changes of the five basic tastes.

In addition to sweet, salty, bitter, and sour, a novel taste that is referred to by the Japanese word *umami* has come to be recognized as a "fifth taste".[4–7] *Umami* taste is found in a diversity of foods like fish, meat, milk, tomato, and some vegetables,[5] and considered to have an important role in the determination of food palatability as well as the intake of food.[8] In Japan, palatable and flavor enhancing taste is given a descriptor word *umami*, which means delicious. In 1908 Ikeda[9] extracted the glutamic acid from seafood and firstly put forward the conception of independent *umami* taste. Unfortunately, *umami* was not internationally accepted as a basic taste because it was supposed that *umami* could be duplicated with appropriate combinations of the other four basic tastes. However, Ikeda's pioneering opinion can be much supported by recent researches. According to the excellent review of taste that was recently published,[10] *umami* is considered to be one of the five basic tastes.

The relationship between changes in the taste recognition threshold for the new taste *umami* and the timing of radiation were analyzed.

Materials and methods

The subjects were 52 patients who underwent RT for their head and neck cancers at the Tokyo University Hospital from April 2002 to August 2007. None of the patients was treated with surgery prior to RT. The malignancies were distributed among the 52 patients as follows: nasopharyngeal cancer, 5; oropharyngeal and hypopharyngeal cancer, 1; oropharyngeal cancer, 17; hypopharyngeal cancer, 20; and the other head and neck cancers, 9. The mean age was 64 years (range, 29–89 years). There were 46 men and six women. Most patients were in good general condition {the 90% rate of Karnofsky performance status was 69% (36/52)}. In most patients (48/52), the RT was administered as a dose of 2 Gy once a day, five times each week. The total RT period ranged from 38 to 62 days (median: 47 days). Conventional radiation technique was used in this study. Only photon energy was used. Off-cord reductions were performed at 40 Gy in 20 fractions. The anterior oral tongue was deflected from the radiation volume after off-cord reduction. Concurrent chemotherapy was allowed in this study. Thirty-three subjects (63%) underwent chemotherapy combined with RT.

The cancers were limited to the head and neck area. Patients who had only a part of tongue within the radiation field were excluded from the study.

LINAC (6 MV in most cases) was used as a radiation source. In most cases, from the start to 40 Gy in 20 fractions, the radiation method was in three fields (their gantry angles were 0, 80, and 280° and beam weight was 1:1:1) in order to include the bilateral whole neck lymph nodes within radiation field. The radiation treatment of the nasopharyngeal and hypopharyngeal cancer also included the oral tongue within the volume of tissue radiated. That is why all patients received radiation dose of at least 11.4 Gy to the anterior tongue. After that, up to 60 Gy in 30 fractions, two shrinking and right and left opposing fields were used. In addition, the radiation field to the tumor bed was reduced. Most patients received a total radiation dose of 72 Gy in 36 fractions (mean: 68.4 Gy, range of dose: 36–72 Gy). The determination of the radiation fields was confirmed with linacgraphy. The planning was based on a three-dimension CT in all patients.

No tumor ablative procedures, or alteration of altering salivary beds, were performed in this study. No patients were taking Salagen or amifostine. None of the enrolled subjects had total or partial glossectomies.

All subjects gave written informed consent before entry into the study. The subjects had no intercurrent illnesses that affected salivary function (i.e., Sjögren's syndrome, human immunodeficiency virus [HIV]). No concurrent medicines altering the taste of the subjects were administered.

The taste recognition threshold for *umami* was measured using the whole-mouth taste method. Test solutions of monosodium glutamate (MSG; 25, 50, 75, or 100 mM) were prepared, and the subjects were tested with 10 mL of each concentration for a recognition threshold. First, the subject was asked to rinse mouth with distilled water and perceive the *umami* taste of the distilled water. Then, using a polyethylene pipette, 10 mL solution of the lowest concentration of one taste was circularly dropped into the mouth of the subject. The subject was instructed to identify the taste and then spat out the solution. When a wrong response was made, the next higher concentration would be applied. The lowest concentration that the subject continuously recognized the stimuli for two times was defined as the recognition threshold.

These taste recognition threshold measurements were performed once before RT and weekly thereafter from the first week to 10–12 weeks after the start of RT. At the same time, the subjects were questioned about xerostomia and mucositis by the radiation oncologists weekly.

Xerostomia or mouth dryness was classified into grade 0, normal; grade 1, mild and slight dryness of mouth, or symptomatic (dry or thick saliva) without significant dietary alteration; grade 2, moderate dryness of mouth, or symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); and grade 3, complete dryness of mouth, or symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated. Stomatitis due to radiation was classified into grade 1, erythema of the mucosa or minimal symptoms, normal diet; grade 2, patchy ulcerations or symptomatic but can eat and swallow modified diet; grade 3, confluent ulcerations or bleeding with minor trauma or symptomatic and unable to adequately aliment or hydrate orally; and grade 4, tissue necrosis, significant spontaneous bleeding, or symptoms associated with life-threatening consequences.

Results

Patients

The mean and median total doses of RT for tip of the tongue were 13.5 Gy and 13.3 Gy (range, 11.4–14.8 Gy) and for the

posterior part of the tongue were 68.4 Gy and 70 Gy (range, 36–72 Gy). The median dose to the affected side of salivary glands was 64 Gy.

Salivary function of the subjects was normal before treatment, but most subjects complained of xerostomia and/or stomatitis from the third week after the start of RT. Grade 3 of xerostomia and/or stomatitis occurred in approximately half of patients (29/52).

Taste recognition

In twenty-five patients (48%), the taste recognition threshold for *umami* did not fall and retained the state of the pre-RT. In the other patients (52%), the threshold deteriorated at the 2nd–5th weeks (median: the 3rd). Figure 1 shows changes in the taste recognition threshold for *umami* every week during and after RT. The sensitivity of taste declined significantly between the start of testing and the 3rd week after beginning RT (at 30 Gy) when compared with the state immediately before the start of RT ($p = 0.0027$). The paired t-test was used in calculating these values. The significance level was set at 0.05. On the 8th week after the start of RT, the sensitivity of taste improved significantly.

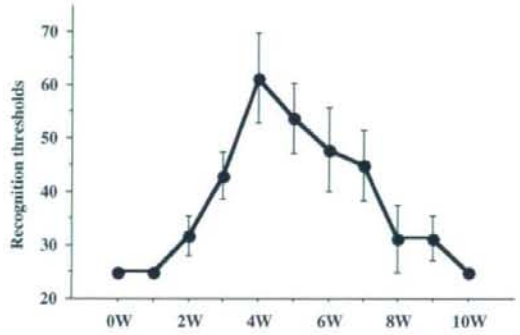

Figure 1 Weekly recognition thresholds of *umami* taste during and after radiation therapy, shown by mean ± SD of the concentration numbers.

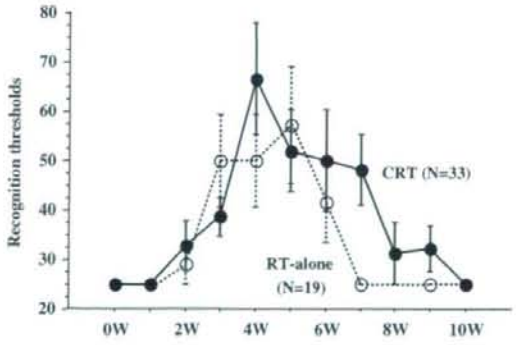

Figure 2 Weekly recognition thresholds of *umami* taste during and after radiation therapy, shown by mean ± SD of the concentration numbers divided by with or without chemotherapy.

In 15 of 34 patients given concurrent chemotherapy (44%), the threshold did not fall. On the other hand, the threshold deteriorated in eight of 18 patients without chemotherapy (44%). Consequently, there was no difference in the effect with and without chemotherapy (Fig. 2).

Discussion

The findings of a prospective study are provided that examines altered taste in patients who are receiving RT with or without chemotherapy for head and neck cancers. This entity of altered taste appears to bother patients but is very much understudied with only a relatively small number of publications occurring over the last few years. Moreover, the *umami* taste quality is only recently recognized and, to my knowledge, there is only one previous report studying taste loss of the *umami* taste during and after RT.[11] Thus, the present study is thought to represent interesting work and new information on the subject.

As shown in our previous reports,[12,13] there was a significant impairment of the threshold of all four basic tastes (sweet, sour, salt, and bitter) at 3 weeks after starting RT, and this impairment continued for 8 weeks. In the present study, the thresholds of *umami* taste increased significantly after irradiation at 3 weeks and recovered at 8 weeks. The impairment pattern was similar to that of 4 basic tastes. This result came up to our expectations. No difference is expected between the impacts of RT on for example sour taste of *umami* taste since there is no different physiology involved, different anatomy.

The reason why only *umami* taste was measured and the 4 other tastes were not evaluated is that the taste disc method on the 4 basic tastes is covered by health insurance in Japan. On the contrary, since there is no taste disc on *umami* taste, we used the whole-mouth method. This is why we presented the result of only *umami* taste in the present study.

In this study, some patients (actually 48%) showed no decline in *umami* taste. There was no link with irradiated dose or other medications. The reason was supposed that the taste recognition threshold for *umami* was measured using the whole-mouth taste method. The whole-mouth method cannot detect the subtle difference in taste threshold compared with the taste disc method and so on.

Treatment of mucositis did not impact the measurement. Pain medications such as non-steroidal anti-inflammatory drugs or oral morphine drugs as the treatment of mucositis have been used. Xerostomia may be an important contributor to *umami* taste.

Antineoplastic drugs that have been associated with taste changes include cisplatin, carboplatin, cyclophosphamide, doxorubicin, 5-fluorouracil, levamisole, and methotrexate.[14] But in this study, as shown in Figure 2, antineoplastic drugs had no or little effect on these patients. Xerostomia, which can be due to RT, may be responsible for taste changes. Damage to salivary glands may reduce the flow of saliva to such an extent that taste substances are not diluted and do not reach the receptor, which may result in food that is tasteless.[14] Changes in the oral flora, with overgrowth of fungi, some bacterial species, and increased dental caries may also lead to altered taste.[15]

Table 1 Wilcoxon signed-rank test comparing with 0 weeks

	0 W	1 W	2 W	3 W	4 W	5 W	6 W	7 W	8 W	9 W
p-value		–	0.0831	0.0027	0.0006	0.0009	0.0172	0.0104	0.3434	0.1679
Mean	25	25	32	43	61	54	48	45	31	31
SD	0	0	18	19	39	30	27	25	13	12

A similar study has previously been published. Shi et al. in Kyushu University[11] first observed the alteration of *umami* taste in patients following head and neck irradiation. In their study, the thresholds of *umami* taste increased after irradiation at 15 Gy. Then, unlike the classic four basic tastes, *umami* taste showed a significant impairment at 30 Gy and reached the peak of mean threshold at 45 Gy. Among the five basic tastes, *umami* taste showed a distinctive pattern of impairment. On the contrary, the distinctive pattern of impairment comparing with the other four basic tastes cannot be found. Our previous study[13] suggested that the other four basic tastes also showed the same pattern of impairment and recovery as *umami*.

In the present study, the recognition thresholds are nearly totally recovered at week eight after the start of RT. Since the treatment took seven weeks, the acute side effects including radiation mucositis or xerostomia were expected to be maximal at week eight. However, the taste thresholds were already largely recovered. It may be because the anterior tip of the tongue was no longer in the radiation fields from 40 Gy (week four) (see Table 1).

According to our previous report,[12] the taste loss is likely to be caused by damage to the taste cells but not by an impairment of the taste nerve fibers. Shatzman and Mossman[16] studied the effects of irradiation on preparations of enriched bovine taste bud membranes by using differential and sucrose gradient centrifugation. They found that a radiation dose of 70 Gy reduced the protein content in the membrane-enriched fraction. However, radiation seemed to have no effect on the amount of cyclic adenosine monophosphate (AMP), which is bound to the membrane and acts as a second messenger. These results suggest that radiation may cause a structural change in the membranes of the taste buds, but the membranes remain normal with respect to function, which is consistent with the suprathreshold taste performance results in this study. If the taste cell membranes and nerve fibers function normally after irradiation, the function of taste intensity–concentration curves should not change significantly.

Umami taste is now recognized as the fifth basic taste category in mammals. It has been suggested that this taste category evolved to enhance detection of amino acids (e.g. glutamate and aspartate) and oligopeptides in foods.[17–19] Monosodium glutamate (MSG) is a prototypic *umami* substance that is widely used as a research tool and flavor enhancer.[5,8,20,21] Preclinical studies have indicated that MSG solutions may evoke *umami* taste through interactions with G-protein-coupled taste receptor (T1R1/T1R3)[21] and/or a ligand activated ion channel[22–24] expressed in taste receptor cells. The taste response to MSG is not observed in T1R1/T1R3 knockout mice.[25] Therefore, this may suggest that irradiation damages the function of taste receptor expression cells.

Taste thresholds are influenced by the quality and quantity of the saliva, which especially by the use of parotid sparing techniques recovers in the year after RT. So it would be very interesting to repeat the test two months, six months and/or one year after RT. This is the subject of a following study. It has been shown several other authors that taste recovers slowly up to one year after treatment.[26]

Comparison with our own previous study with another patients and another method (i.e. disc method)[12], during head and neck irradiation the clinical impairment of *umami* taste is not different from that of the other four basic tastes. Shi et al.[11] concluded the opposite. They did find a different impairment pattern of the *umami* taste compared to the other taste qualities.[11] This reason might be that Shi et al.[11] examined only up to the 60 Gy and additionally only at the time point of pre-RT, 15, 30, 45, and 60 Gy and, on the other hand, we performed taste test every week from pre-RT to 9 weeks. Other authors[27,28] have found that the bitter and/or salt taste quality were affected most as compared to sweet and sour.

With the implementation of new radiation techniques, such as conformal and intensity-modulated RT (IMRT) in head and neck irradiation, the late-radiation effects can probably be reduced since these new techniques become more and more standard and since these techniques reduce the radiation dose to the salivary gland tissue and to the oral tongue. As shown in our previous report,[13] the importance of the irradiated tongue volume in relation to taste changes. In the group including most of the tongue within the radiation fields, there was a significant impairment and improvement of the threshold of all four basic tastes. However, this was not seen in the group not including the tip of the tongue within the radiation fields. According to Fang et al.,[29] the exception was that patients treated by IMRT had a both statistically and clinically significant improvement in global QOL, fatigue, taste/smell, dry mouth, and feeling ill at the time point of 3 months after RT. These modified techniques may result in a reduced number of taste buds irradiated and thus, might be helpful to preserve taste function against radiation damage. This QOL study show that taste loss is a significant chronic complication of head and neck therapy. The present study is a short-term assessment of taste impairment and recovery only by the end of RT or immediately after RT. We are planning to continue this taste test in patients who are followed up after completing RT.

Conflict of interest statement

None declared.

Acknowledgments

The excellent technical assistance of Chigusa Nagai and Mayuko Onimura in taste testing is gratefully acknowledged.

References

1. Mossman K, Shatzman A, Chencharick J. Long-term effects of radiotherapy on taste and salivary function in man. *Int J Radiat Oncol Biol Phys* 1982;**8**:991–7.
2. Bolze MS, Fosmire GJ, Stryker JA, Chung CK, Flipse BG. Taste acuity, plasma zinc levels, and weight loss during radiotherapy, a study of relationships. *Radiology* 1982;**144**:163–9.
3. Semba SW, Mealey BL, Hallamon WW. The head and neck radiotherapy patient: part 1-oral manifestations of radiation therapy. *Compendium* 1994;**15**:250–60.
4. Baylis LL, Rolls ET. Responses of neurons in the primate taste cortex to glutamate. *Physiol Behav* 1991;**49**:973–9.
5. Yamaguchi S. Basic properties of *umami* and effects on humans. *Physiol Behav* 1991;**49**:833–41.
6. Yamamoto T, Asai K, Kawamura Y. Studies in responses of cortical taste neurons to *Umami* substances. In: Kawamura Y, Kare MR, editors. *Umami a basic taste*. New York: Marcel Dekker; 1987. p. 441–60.
7. Bellisle F. Glutamate and the *umami* taste: sensory, metabolic, nutritional and behavioral considerations. A review of the literature published in the last 10 years. *Neurosci Biobehav Rev* 1999;**23**:423–38.
8. Yamaguchi S, Ninomiya K. *Umami* and food palatability. *J Nutr* 2000;**130**:s921–6.
9. Ikeda K. On a new seasoning. *J Tokyo Chem Soc* 1909;0: 820–36.
10. Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. *Nature* 2006;**444**: 288–94.
11. Shi HB, Masuda M, Umezaki T, Kuratomi Y, Kumamoto Y, Yamamoto T, et al. Irradiation impairment of *umami* taste in patients with head and neck cancer. *Auris Nasus Larynx* 2004; **31**:401–6.
12. Yamashita H, Nakagawa K, Tago M, Nakamura N, Shiraishi K, Eda M, et al. Taste dysfunction in patients receiving radiotherapy. *Head Neck* 2006;**28**:508–16.
13. Yamashita H, Nakagawa K, Nakamura N, Abe K, Asakage T, Ohmoto M, et al. Relation between acute and late irradiation impairment of four basic tastes and irradiated tongue volume in patients with head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2006;**66**:1422–9.
14. Wickham RS, Rehwaldt M, Kefer C, Shott S, Abbas K, Glynn-Tucker E, et al. Taste changes experienced by patients receiving chemotherapy. *Oncol Nurs Forum* 1999;**26**:697–706.
15. Fernando IN, Patel T, Billingham L, Hammond C, Hallmark S, Glaholm J, et al. The effect of head and neck irradiation on taste dysfunction: a prospective study. *Clin Oncol (R Coll Radiol)* 1995;**7**:173–8.
16. Shatzman AR, Mossman KL. Radiation effects on bovine taste bud membranes. *Radiat Res* 1982;**92**:353–8.
17. Bellisle F. Glutamate and the *umami* taste: sensory, metabolic, nutritional and behavioural considerations. *Neurosci Biobehav Rev* 1999;**23**:423–38.
18. Brand JG. Receptor and transduction processes for *umami* taste. *J Nutr* 2000;**130**:942s–5s.
19. Doty RL. *Handbook of olfaction and gustation*. New York: Marcel Dekker, Inc.; 2003.
20. Kobayashi C, Kennedy LM. Experience-induced changes in taste identification of monosodium glutamate. *Physiol Behav* 2002;**75**:57–63.
21. Nelson G, Chandrashekar J, Hoon MA, et al. An aminoacid taste receptor. *Nature* 2002;**416**:199–202.
22. Toyono T, Seta T, Kataoka S, et al. Expression of metabotropic glutamate receptor group I in rat gustatory papillae. *Cell Tissue Res* 2003;**313**:29–35.
23. Chaudhari N, Landin AN, Roper SD. A metabotropic glutamate receptor variant functions as a taste receptor. *Nat Neurosci* 2000;**3**:113–9.
24. Nakashima K, Katsukawa H, Sasamoto K, et al. Behavioral taste similarities and differences among monosodium L-glutamate and glutamate receptor agonists in C57BL mice. *J Nutr Sci Vitaminol* 2001;**47**:161–6.
25. Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, Ryba NJ, et al. The receptors for mammalian sweet and *umami* taste. *Cell* 2003;**115**:255–66.
26. Ruo Redda MG, Allis S. Radiotherapy-induced taste impairment. *Cancer Treat Rev* 2006;**32**:541–7.
27. Zheng WK, Inokuchi A, Yamamoto T, Komiyama S. Taste dysfunction in irradiated patients with head and neck cancer. *Fukuoka Igaku Zasshi* 2002;**93**:64–76.
28. Maes A, Huygh I, Weltens C, Vandevelde G, Delaere P, Evers G, et al. De Gustibus: time scale of loss and recovery of tastes caused by radiotherapy. *Radiother Oncol* 2002;**3**:195–201.

[29]. LinksFang FM, Chien CY, Tsai WL, Chen HC, Hsu HC, Lui CC, et al. Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy – a longitudinal study. *Int J Radiat Oncol Biol Phys*; 2008 March 18 [Epub ahead of print].

Acta Oncologica, 2009; 48: 314–318

informa
healthcare

LETTERS TO THE EDITOR

Contrast media-assisted visualization of brain metastases by kilovoltage cone-beam CT

HIROSHI IGAKI[1], KEIICHI NAKAGAWA[1], HIDEOMI YAMASHITA[1], ATSURO TERAHARA[1], AKIHIRO HAGA[1], KENSHIRO SHIRAISHI[1], NAKASHI SASANO[1], KENTARO YAMAMOTO[1], TSUYOSHI ONOE[1,2], KIYOSHI YODA[3] & KUNI OHTOMO[1]

[1]*Department of Radiology, University of Tokyo Hospital, Tokyo, Japan,* [2]*Department of Radiation Oncology, Cancer Institute Hospital, Tokyo, Japan and* [3]*Elekta, KK, Kobe, Japan.*

To the Editor

The latest linear accelerator equipped with a kilovoltage (kV) cone-beam CT (CBCT) unit is useful for registration at the time of treatment, and thus reduces the setup error [1–4]. But in the case of intracranial or abdominal tumors, the contours of the tumors are difficult to determine on the CT images without contrast media, since such tumors are located next to normal soft tissue whose Hounsfield unit is close to those of the tumors themselves.

Image registration by CBCT is performed based on the bony structures or soft tissue around the tumor. But this process does not necessarily guarantee that the position of the isocenter at treatment is identical with that at the time of planning CT, since bone or soft-tissue registration is based on a volume-matching process. It is difficult to know the exact tumor location for a low-contrast tumor even if on-board registration of the tumor is intended, since the tumor contour is not well visualized even on planning CT images without contrast media. We attempted to visualize metastatic brain

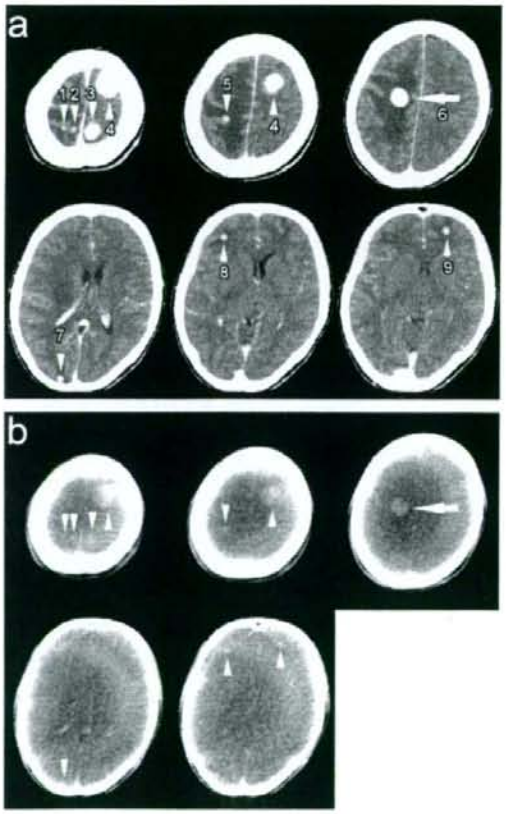

Figure 1 (*Continued*)

Figure 1. Brain tumor images acquired by planning CT (a) and kV CBCT (b) after each intravenous bolus administration of iodized contrast media. The treatment isocenter was set within the tumor indicated by the arrow. Tumors are indicated by the arrowhead. All tumors 6 mm or more in the greatest dimension in the planning CT (a) were also detectable in the CBCT (b). The numbers assigned in the tumor correspond to those in Table I.

Correspondence: Keiichi Nakagawa, Department of Radiology, University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. Tel: +81 3 5800 8666. Fax: +81 3 5800 8786. E-mail: k-nak@fg7.so-net.ne.jp

(Received 6 June 2008; accepted 30 June 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802310983

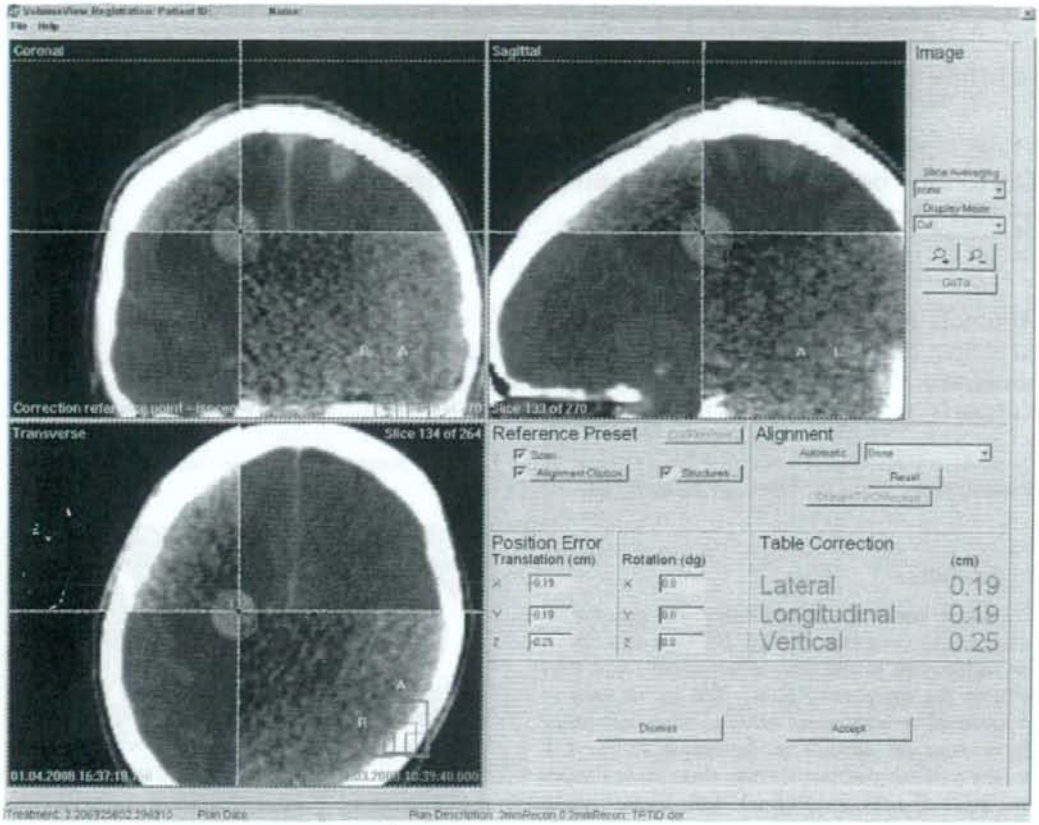

Figure 2. The desktop screen at the time of image registration. After bone registration, the location of the tumor at the isocenter was verified by eye and registered well.

tumors by contrast media administration in kV CBCT images.

A 41-year-old female developed multiple brain metastases from a follicular variant of papillary carcinoma of the thyroid. Radiotherapy planning was performed by Pinnacle[3] (Philips/ADAC, Milpitas, CA) based on CT images acquired by a large-bore CT (Aquilion/LB, Toshiba, Tokyo, Japan) after an intravenous bolus injection of 100 ml of iodized contrast media, Iopamiron 300 (Schering, Berlin,

Table I. Characteristics of the tumors observed in the planning CT.

Tumor No.[1]	Size (mm)[2]	Locus	Possible factors interfering with detectability in CBCT [8]
1	6 × 4	Rt. high frontal	Cupping artifacts Ring artifact
2	7 × 5	Rt. high frontal	Cupping artifacts Ring artifact
3	18 × 16	Lt. high frontal	Cupping artifacts Ring artifact
4	27 × 19	Lt. high frontal	Cupping artifacts Ring artifact
5	7 × 7	Rt. high frontal	Cupping artifacts
6	19 × 16	Rt. frontal	–
7	8 × 8	Rt. occipital	Cupping artifacts
8	7 × 7	Rt. frontal tip	Ring artifact
9	8 × 8	Lt. frontal tip	Ring artifact
10	4 × 4	Lt. frontal	Cupping artifacts Ring artifact

[1]The numbers of the tumors correnspond to those in Figure 1.
[2]Sizes were measured on 5-mm-thick images of the planning CT.
The greatest dimension and its orthogonal dimension in the axial slice was presented.

Germany). Elekta Synergy (Elekta, Crawley, England), equipped with kV CBCT unit, was used for registration and treatment. Immediately before the treatment, on-board CBCT images were taken four minutes after another intravenous bolus injection of 100 ml of Iopamiron 300. The initial estimation of the tumor registration was performed by built-in bone-matching software because it was very quick. Subsequently, the tumor position in the CBCT image and the isocenter imported from the treatment planning system were displayed for further manual adjustment by eye. Written informed consent on these procedures and treatment was obtained from the patient.

Figure 1a presents representative axial images of the planning CT of this patient. Figure 1b shows kV CBCT images of the corresponding slices taken immediately before the treatment. The isocenter was set within the tumor in the right frontal lobe indicated by the arrow in the Figure 1a. No further manual adjustment was performed after bone matching in this study. The tumor position was directly registered (Figure 2). Thus, it was shown that direct tumor registration was feasible by contrast media-assisted kV CBCT. The patient was treated with whole-brain irradiation.

All the tumors with diameters of 6 mm or more in the greatest dimension observed in the 5-mm-thickness planning CT image were also visible by CBCT (Table I). Ring artifacts of the concentric circle that centers on the treatment isocenter, possibly due to the skull, were seen in the CBCT images (Figure 1b). But these artifacts did not degrade the accuracy of visual verification insofar as the tumor was detectable. Other smaller metastases sized less than 6 mm in the planning CT were undetectable in the CBCT images.

This is the first report of direct tumor visualization and registration in the linear accelerator-mounted CBCT by contrast media administration. It had been reported that sufficient soft-tissue contrast could not be obtained in kV CBCT images by contrast media administration [5]. This is an obstacle for direct tumor registration. To overcome this difficulty, Guckenberger et al. used mobile in-room CT with contrast media just before the treatment [5,6]. The idea of their report is interesting, but the tumor image obtained by in-room CT does not warrant exact tumor position during the treatment. Through our procedure, we can know the exact position of the small tumor itself in an organ with soft-tissue density on-board even during the treatment by simultaneous dual exposure of kV x-ray for CBCT and megavoltage x-ray for treatment [4]. In addition, we determined the minimum size of brain tumors that can be visualized by kV CBCT in this study.

Metastatic brain tumors 6mm or more in the greatest dimension were visualized in the CBCT. This means that tumors 6 mm or more in the greatest dimension are candidates for direct tumor registration by contrast media-assisted kV CBCT. The possible reasons why smaller tumors could not be detected in the CBCT were low contrast of the image, low resolution of the image, the ring artifacts described above, and artifacts due to beam hardening. Most of them had been pointed out previously [7,8], and some problems have already overcome by improvement of the systems [7].

The tumors of the patient involved in this report were strongly and homogeneously enhanced by contrast media. Such characteristics of the tumor appeared suitable for this procedure of visualization. In our preliminary experience, soft-tissue contrast of cystic tumors or heterogeneously enhanced tumors was insufficient in the CBCT images. It is expected that the radiological characteristics of the tumor influence the minimum size of the tumor that can be visualized by CBCT. In the future, we should clarify such relationships by further studies incorporating more patients.

Conflict of Interest Statement

Dr. Nakagawa receives research funding from Elekta K.K. All other authors have no financial or personal relationship with other people or organizations that could inappropriately influence this work.

References

[1] Oldham M, Letourneau D, Watt L, Hugo G, Yan D, Lockman D, et al. Cone-beam-CT guided radiation therapy: A model for on-line application. Radiother Oncol 2005;75: 271–8.

[2] Boda-Heggemann J, Walter C, Rahn A, Wertz H, Loeb I, Lohr F, et al. Repositioning accuracy of two different mask systems-3D revisited: Comparison using true 3D/3D matching with cone-beam CT. Int J Radiat Oncol Biol Phys 2006; 66:1568–75.

[3] Thilmann C, Nill S, Tucking T, Hoss A, Hesse B, Dietrich L, et al. Correction of patient positioning errors based on in-line cone beam CTs: Clinical implementation and first experiences. Radiat Oncol 2006;1:16.

[4] Nakagawa K, Yamashita H, Shiraishi K, Igaki H, Terahara A, Nakamura N, et al. Verification of in-treatment tumor position using kilovoltage cone-beam computed tomography: A preliminary study. Int J Radiat Oncol Biol Phys 2007;69: 970–3.

[5] Guckenberger M, Baier K, Guenther I, Richter A, Wilbert J, Sauer O, et al. Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. Int J Radiat Oncol Biol Phys 2007;69:294–301.

[6] Guckenberger M, Sweeney RA, Wilbert J, Krieger T, Richter A, Baier K, et al. Image-guided radiotherapy for liver cancer using respiratory-correlated computed tomography and cone-

beam computed tomography. Int J Radiat Oncol Biol Phys 2008;71:297–304.
[7] Letourneau D, Wong JW, Oldham M, Gulam M, Watt L, Jaffray DA, et al. Cone-beam-CT guided radiation therapy: Technical implementation. Radiother Oncol 2005;75:279–86.
[8] Barrett JF, Keat N. Artifacts in CT: Recognition and avoidance. Radiographics 2004;24:1679–91.

Small cell carcinoma of unknown primary presenting with disease confined to the central nervous system

FIONA CHIONH, ARUN AZAD & CHOOI LEE

Andrew Love Cancer Centre, Barwon Health, Geelong Hospital

To the Editor

We refer to an article published recently in your journal [1], in which the authors stated that extrapulmonary small cell carcinoma (EPSCC) "has been recognized at all sites of the body except the central nervous system". We disagree with this statement and find it ambiguous. If the authors are referring to EPSCC with brain metastases, we argue that this in fact has been widely described [2–9].

Small cell carcinoma of unknown primary (SCUP) is a subset of EPSCC, constituting between 8% [10] to 31% [11] of all EPSCC diagnoses. If the authors are referring to SCUP presenting with central nervous system (CNS) disease, although rare, we have identified one previously reported case in the literature [10]. Furthermore, our institution has recently treated two patients with SCUP who presented with disease isolated to the CNS and who also experienced relapse in the CNS alone.

Both patients were previous smokers, the first a 56-year-old male and the second a 71-year-old female. Both initially presented with a solitary intracranial lesion that was resected. Histology was consistent with small cell carcinoma, and no other sites of disease were found on staging investigations (computed tomography of the chest, abdomen and pelvis and whole body bone scan). Both patients received whole brain radiotherapy (30 Gy in 10 fractions). After 16 and 21 months respectively, both patients relapsed with isolated spinal intradural extramedullary disease that was surgically debulked. Histology was again consistent with small cell carcinoma. Both patients received radiotherapy to the involved spine (30 Gy in 10 fractions), followed by carboplatin (AUC 5, Day 1) and etoposide (120mg/m^2 Days 1–3) chemotherapy. The first patient completed four cycles and remains alive and well 33 months after the initial diagnosis. The second patient developed pneumonia and an acute myocardial infarction after cycle 1, and died shortly thereafter (24 months after the initial diagnosis). In a recent retrospective study, median survival for SCUP was only 2.5 months [11]. By comparison, our patients experienced prolonged disease-free and overall survival.

In summary, not only does EPSCC metastasise to the brain, but SCUP can also present initially in the CNS as demonstrated by the two cases we have described.

References

[1] Lee SS, Lee JL, Ryu MH, Chang HM, Kim TW, Kim WK, et al. Extrapulmonary small cell carcinoma: Single center experience with 61 patients. Acta Oncol 2007;46:846–51.
[2] Cicin I, Karagol H, Uzunoglu S, Uygun K, Usta U, Kocak Z, et al. Extrapulmonary small-cell carcinoma compared with small-cell lung carcinoma: A retrospective single-center study. Cancer 2007;110:1068–75.
[3] Saeki H, Anegawa G, Masuda T, Ohta R, Honda M, Kai T, et al. A case of inoperable gastric small cell carcinoma effectively treated by chemotherapy and radiotherapy (Japanese). Gan To Kagaku Ryoho 2006;33:977–9.
[4] Koide N, Hiraguri M, Kishimoto K, Nakamura T, Adachi W, Miyabayashi H, et al. Small cell carcinoma of the esophagus with reference to alternating multiagent chemotherapy: Report of two cases. Surg Today 2003;33:294–8.
[5] Shamelian SO, Nortier JW. Extrapulmonary small-cell carcinoma: Report of three cases and update of therapy and prognosis. Neth J Med 2000;56:51–5.
[6] Orhan B, Yalçin S, Evrensel T, Yerci O, Manavoğlu O. Successful treatment of cranial metastases of extrapulmon-

Correspondence: Fiona Chionh, Medical Oncology Unit, Level 6 HSB, Austin Hospital, 145 – 163 Studley Road, Heidelberg, Victoria 3084, Australia

(Received 28 May 2008; accepted 30 June 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802311817

ary small cell carcinoma with chemotherapy alone. Med Oncol 1998;15:66–9.

[7] Khansur TK, Routh A, Mihas TA, Underwood JA, Smith GF, Mihas AA. Syndrome of inappropriate ADH secretion and diplopia: Oat cell (small cell) rectal carcinoma metastatic to the central nervous system. Am J Gastroenterol 1995;90:1173–4.

[8] Zachariah B, Casey L, Zachariah SB, Baekey P, Greenberg HM. Case report: Brain metastasis from primary small cell carcinoma of the prostate. Am J Med Sci 1994;308:177–9.

[9] Hussein AM, Feun LG, Sridhar KS, Otrakji CL, Garcia-Moore M, Benedetto P. Small cell carcinoma of the large intestine presenting as central nervous systems signs and symptoms. Two case reports with literature review. J Neurooncol 1990;8:269–74.

[10] Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer 1997;79:1729–36.

[11] Haider K, Shahid RK, Finch D, Sami A, Ahmad I, Yadav S, et al. Extrapulmonary small cell cancer: A Canadian province's experience. Cancer 2006;107:2262–9.

doi: 10.1111/j.1346-8138.2008.00533.x

LETTER TO THE EDITOR

Interesting response to concurrent chemoradiation in metastatic eccrine porocarcinoma

Dear Editor,

We report a case of a patient with metastatic eccrine porocarcinoma (EP) who has achieved complete remission to date following concurrent chemoradiation therapy. The patient is a 61-year-old man. At age 35 years, he noticed a small 1-cm diameter tumor growth in the front of his left crus. He decided to let it take its own course. The lesion grew slowly up to 3 cm in diameter. At age 55 years, a recommended resection of the red and granulomatous lesion of the lateral surface of his left crus was performed under local anesthesia. The resection was performed with 4-mm margins up to the epifascias. Pathological diagnosis was of invasive EP with squamous differentiation because cellular atypia was high at the center of the lesion and the tumor cells had invaded into the dermis (Fig. 1). In May 2003, the patient became aware of left inguinal swelling. Results of the physical examination fell within normal limits except for a surgical scar measuring 7 cm on the outside of the left thigh. Biopsy of the left inguinal lymph node was performed, and histopathology revealed a metastatic lesion of the EP.

Computed tomography on 4 November 2003 revealed multiple lymph node swellings from the left inguinal and internal iliac to the abdominal paraaortic region. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) on 28 November 2003 (Fig. 2a) revealed regions of increased multiple uptake from the paraaortic to the regions of the left iliac and left femoral arteries, and the left inguinal region (standardized uptake values of maximum-valued pixel within the tumor, [SUV-max], 4.5–6.6; average, 2.9–3.9).

Chemotherapy consisted of cisplatin (75 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 per 24 h by continuous infusion from days 1–4).[1] This chemotherapy regimen was repeated every 3 weeks and was administered in two courses. Abdominal irradiation was performed with 6-MV photons from a linear accelerator in our institution. Radiation therapy began on day 1 (6 January 2004) with a dose of 50.4 Gy in 28 fractions over 5.6 weeks without an interval. The radiation field was defined as the area

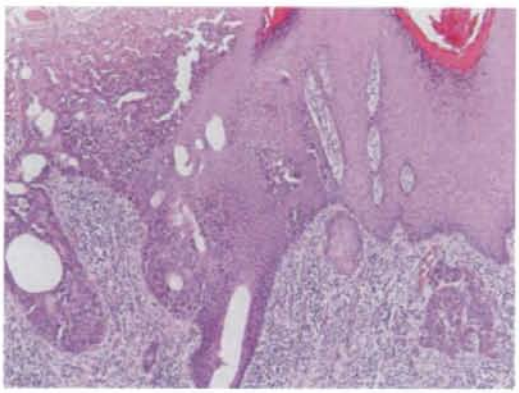

Figure 1. Histopathological examination revealed an ulcerated tumor at the center of which tumor cells were noted with obvious nuclear enlargement and irregularity in size. The tumor cells had invaded into the surface layer of the dermis and proliferated forming medium- and small-sized alveolar nests. The alveolar nests showed keratinization and cavity formation that included an amorphous substance. At the marginal zone of the lesion, atypia of the tumor cells became weak and, in the epidermis, poroid tumor cells with relatively clear borders formed proliferating nests. Pathological diagnosis was invasive eccrine porocarcinoma with squamous differentiation because cellular atypia was high at the center of the lesion and the tumor cells had invaded into the dermis.

Correspondence: H. Yamashita, M.D., Ph.D., Department of Radiology, University of Tokyo Hospital, 7-3-1 Hongo, Bunnkyou-ku, Tokyo 113-8655, Japan. Email: yamashitah-RAD@h.u-tokyo.ac.jp

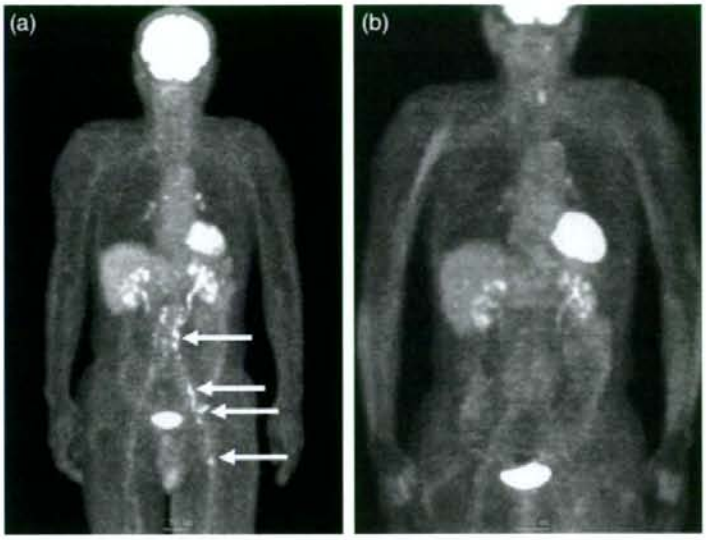

Figure 2. Front image of fluorine-18 fluorodeoxyglucose positron emission tomography (a) pre- and (b) post-treatment. In the pretreatment positron emission tomography, multiple uptake increasing regions from paraaortic to left iliac artery region, left inguinal region and left femoral artery region were seen (arrows).

that contained the uptake increasing regions in FDG-PET, with a margin of 20 mm. After initial irradiation with a dose of 41.4 Gy in 23 fractions, off-cord four-port box fields were used. This treatment was tolerated well.

Computed tomography of the abdomen, pelvis and bilateral femurs with i.v. enhancement on both 1 March 2004 and 28 July 2004 revealed no definitive evidence of metastasis. After the combined therapy, complete remission was noted according to the FDG-PET study (Fig. 2b). This result indicates that chemoradiation therapy is an alternative treatment for metastatic EP.[2–5]

Hideomi YAMASHITA,[1] Takafumi KADONO,[2] Kunihiko TAMAKI,[2] Keiichi NAKAGAWA[1]
Departments of [1]Radiology, and [2]Dermatology, University of Tokyo Hospital, Tokyo, Japan

REFERENCES

1 Minsky BD, Pajak TF, Ginsberg RJ *et al.* INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; **20**: 1167–1174.
2 Bellman B, Gregory NA, Silvers D *et al.* Sweat gland carcinoma with metastases to the skin: response to 5-fluorouracil chemotherapy. *Cutis* 1995; **55**: 221–224.
3 Plunkett TA, Hanby AM, Miles1 DW *et al.* Metastatic eccrine porocarcinoma: response to docetaxel (Taxotere) chemotherapy. *Annuls Oncol* 2001; **12**: 411–414.
4 Coonley CJ, Kelsen VP, Huvos AG *et al.* Chemotherapy of eccrine sweat gland carcinoma. A retrospective review. *J Clin Oncol* 1985; **8**: 307–311.
5 Turn Gonzalez-Lopez MA, Zquez-Lopez FVA, Soler TS *et al.* Metastatic eccrine porocarcinoma: a 5.6-year follow-up study of a patient treated with a combined therapeutic protocol. *Dermatol Surg* 2003; **29**: 1227–1232.

Urethral Dose and Increment of International Prostate Symptom Score (IPSS) in Transperineal Permanent Interstitial Implant (TPI) of Prostate Cancer

Naoya Murakami[1,2], Jun Itami[1,2], Kae Okuma[1], Hiroshi Marino[1], Keiichi Nakagawa[3], Tsukasa Ban[1], Moritoshi Nakazato[1], Kazuyoshi Kanai[1], Kuniji Naoi[1], Masashi Fuse[1]

Purpose: To find the factors which influence the acute increment of International Prostate Symptom Score (IPSS) after transperineal permanent interstitial implant (TPI) using ^{125}I seeds.

Patients and Methods: From April 2004 through September 2006, 104 patients with nonmetastatic prostate cancer underwent TPI without external-beam irradiation. Median patient age was 70 years with a median follow-up of 13.0 months. 73 patients (70%) received neoadjuvant hormone therapy. The increment of IPSS was defined as the difference between pre- and postimplant maximal IPSS. Clinical, treatment, and dosimetric parameters evaluated included age, initial prostate-specific antigen, Gleason Score, neoadjuvant hormone therapy, initial IPSS, post-TPI prostatic volume, number of implanted seeds, prostate V_{100}, V_{150}, D_{90}, urethral D_{max}, and urethral D_{90}. In order to further evaluate detailed urethral doses, the base and apical urethra were defined and the dosimetric parameters were calculated.

Results: The IPSS peaked 3 months after TPI and returned to baseline at 12–15 months. Multivariate analysis demonstrated a statistically significant correlation of post-TPI prostatic volume, number of implanted seeds, and the dosimetric parameters of the base urethra with IPSS increment.

Conclusion: The base urethra appears to be susceptible to radiation and the increased dose to this region deteriorates IPSS. It remains unclear whether the base urethral dose relates to the incidence of late urinary morbidities.

Key Words: Prostate cancer · International Prostate Symptom Score (IPSS) · Seed implant · ^{125}I · Urethral dose

Strahlenther Onkol 2008;184:515–9
DOI 10.1007/s00066-008-1833-3

Urethraldosis und Erhöhung des International Prostate Symptom Score (IPSS) bei transperinealer permanenter interstitieller Brachytherapie des Prostatakarzinoms

Ziel: Ermittlung von Parametern, die nach einer transperinealen permanenten interstitiellen Brachytherapie der Prostata mit ^{125}I eine Zunahme des International Prostate Symptom Score (IPSS) bewirken.

Patienten und Methodik: Von April 2004 bis September 2006 erhielten 104 Patienten mit nichtmetastasiertem Prostatakarzinom eine alleinige transperineale permanente interstitielle Brachytherapie mit ^{125}I ohne vorherige perkutane Therapie. Das mittlere Patientenalter betrug 70 Jahre, die mediane Beobachtungszeit lag bei 13,0 Monaten. 73 Patienten (70%) erhielten eine neoadjuvante Hormontherapie. Die Erhöhung des IPSS wurde als Differenz zwischen initialem und maximalem IPSS definiert. Analysiert wurden klinische, therapeutische sowie dosimetrische Parameter wie Patientenalter, initialer PSA-Wert (prostataspezifisches Antigen), Gleason-Score, neoadjuvante Hormontherapie, initialer IPSS, Prostatavolumen nach Implantation, Zahl der implantierten ^{125}I-Seeds, die DVH-Parameter V_{100}, V_{150}, D_{90} für die Prostata sowie D_{max} und D_{90} für die Urethra. Zur detaillierten Untersuchung der Urethrabelastung wurden basale und apikale Urethra definiert, für die ebenfalls DVH-Parameter berechnet wurden.

Ergebnisse: Der IPSS erreichte 3 Monate nach ^{125}I-Implantation sein Maximum und kehrte nach 12–15 Monaten wieder auf den Ausgangswert zurück. Eine multivariate Analyse ergab, dass das Prostatavolumen nach Implantation, die Anzahl der implantierten ^{125}I-Seeds und die dosimetrischen Parameter der Basisurethra statistisch signifikant mit der Erhöhung des IPSS korrelierten.

[1] Department of Radiation Therapy and Oncology, International Medical Center of Japan, Tokyo, Japan,
[2] Division of Radiation Therapy, National Cancer Center Hospital, Tokyo, Japan,
[3] Department of Radiology, School of Medicine, Tokyo University, Japan.

Received: January 11, 2008; accepted: July 3, 2008