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.

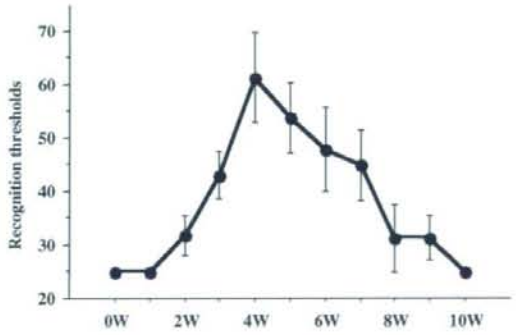

Figure 1 Weekly recognition thresholds of *umami* taste during and after radiation therapy, shown by mean ± SD of the concentration numbers.

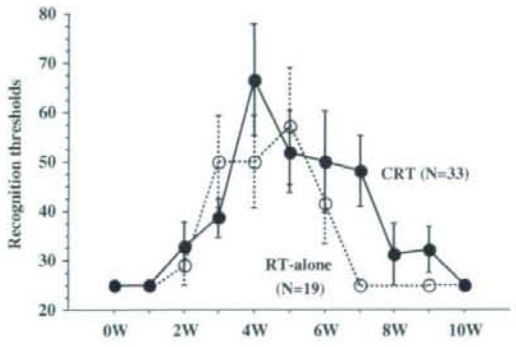

Figure 2 Weekly recognition thresholds of *umami* taste during and after radiation therapy, shown by mean ± SD of the concentration numbers divided by with or without chemotherapy.

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.

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Acta Oncologica, 2009; 48: 314–318

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LETTERS TO THE EDITOR

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

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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

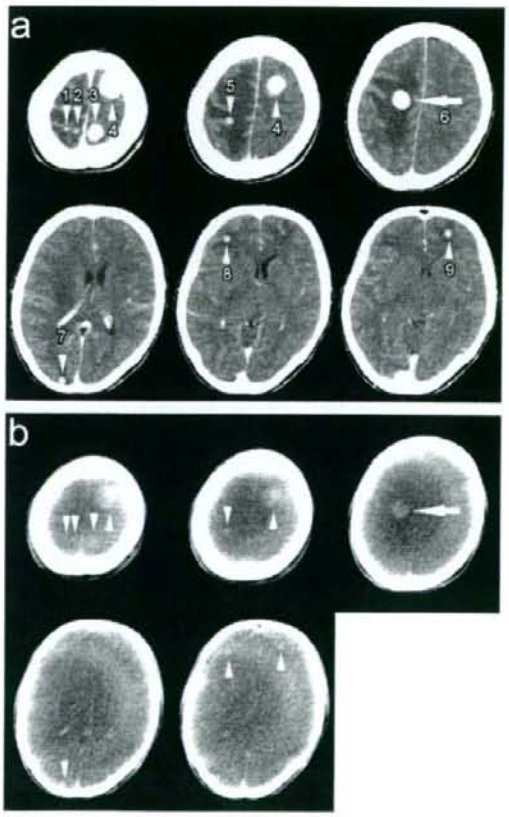

Figure 1. Brain tumor images acquired by planning CT (a) and kV CBCT (b) after each intravenous bolus administration of iodized contrast media. The treatment isocenter was set within the tumor indicated by the arrow. Tumors are indicated by the arrowhead. All tumors 6 mm or more in the greatest dimension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

Figure 1 (*Continued*)

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(Received 6 June 2008; accepted 30 June 2008)

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

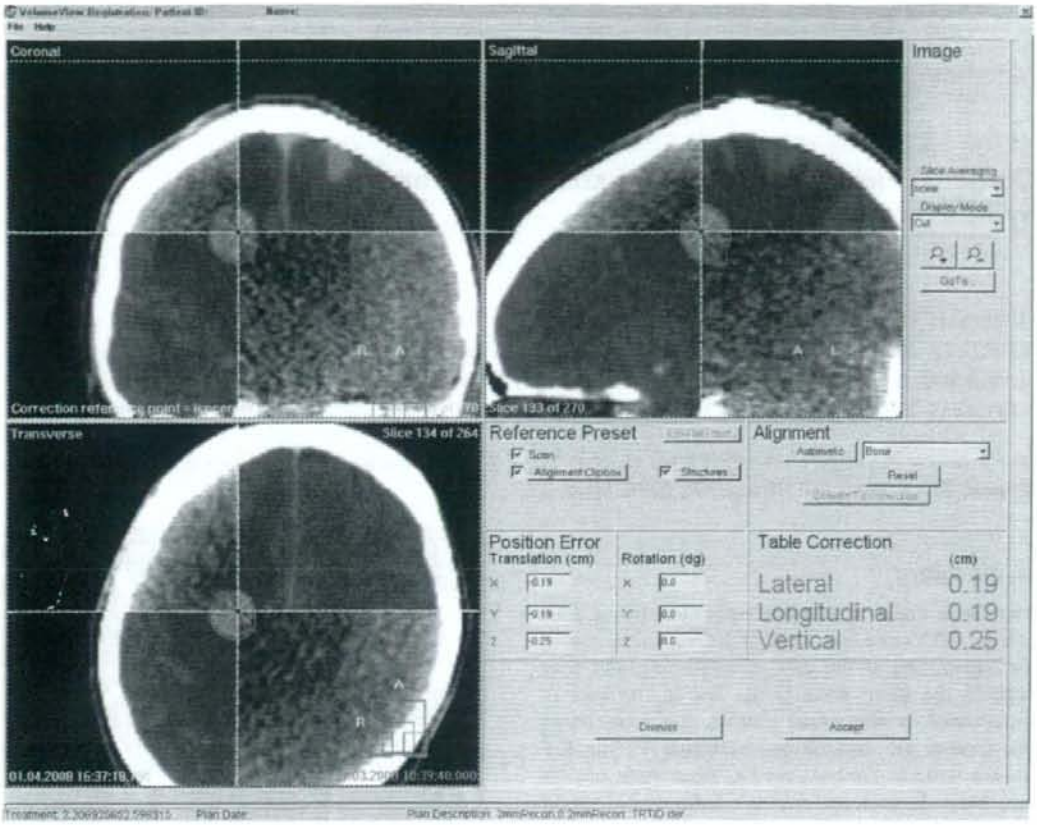

Figure 2. The desktop screen at the time of image registration. After bone registration, the location of the tumor at the isocenter was verified by eye and registered well.

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 1. 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.

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

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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.

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(Received 28 May 2008; accepted 30 June 2008)

ISSN 0284-186X print/ISSN 1651-226X online © 2009 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS)
DOI: 10.1080/02841860802311817

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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

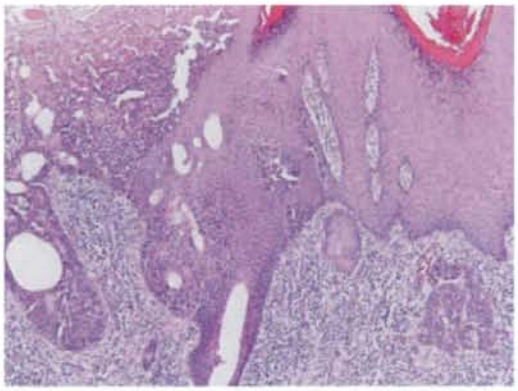

Figure 1. Histopathological examination revealed an ulcerated tumor at the center of which tumor cells were noted with obvious nuclear enlargement and irregularity in size. The tumor cells had invaded into the surface layer of the dermis and proliferated forming medium- and small-sized alveolar nests. 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.

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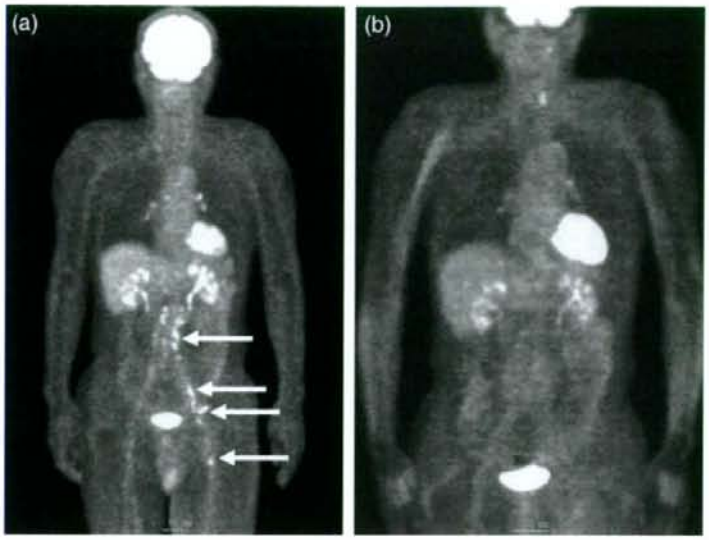

Figure 2. Front image of fluorine-18 fluorodeoxyglucose positron emission tomography (a) pre- and (b) post-treatment. In the pretreatment positron emission tomography, multiple uptake increasing regions from paraaortic to left iliac artery region, left inguinal region and left femoral artery region were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

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

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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.

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

Schlussfolgerung: Die basale Urethra scheint sich als strahlenempfindlich zu erweisen, und die erhöhte Dosis in dieser Region verschlechtert den IPSS. Unklar bleibt, ob die Dosis in der basalen Urethra im Zusammenhang mit dem Auftreten urethraler Spätwirkungen steht.

Schlüsselwörter: Prostatakarzinom · International Prostate Symptom Score (IPSS) · Seed-Implantat · ^{125}I · Urethradosis

Introduction

In the current management with radiotherapy for localized adenocarcinoma of prostate, intensity-modulated radiotherapy [6] and ultrasound-guided transperineal permanent interstitial implant (TPI) using ^{125}I radioactive seeds [2] are widely employed, because both methods satisfy the requirement of dose escalation to achieve biochemical control and reduce dose to the normal tissues. With the clinical experiences accumulated for decades, guidelines on standardized TPI for localized prostate cancer were established [9, 16] and favorable long-term results were achieved [5, 14, 15, 18]. In TPI, acute urinary morbidities are seen in most of the patients and this is reflected in the increment of International Prostate Symptom Score (IPSS). However, introduction of the peripheral or modified peripheral seed placement methods has reduced urethral dose dramatically and the relationship between the urethral dose and the increment of IPSS has been variously reported. In the present study, the detailed urethral doses of TPI were investigated in relation to the acute increment of IPSS.

Patients and Methods

From April 2004 through September 2006, 104 patients with nonmetastatic prostate cancer underwent TPI with documentation of the IPSS before and after the procedure. Patients treated with combined external-beam radiation therapy were excluded from this study. Clinical characteristics of the 104 patients are summarized in Table 1. T-stage according to the International Union Against Cancer (UICC) [17] was defined solely by digital rectal examination without considering information of the radiologic images. We stratified patients according to the Seattle risk classification [18]. The number of patients who received neoadjuvant hormone therapy was 73 (70%) and most of them were started by urologists. Neoadjuvant hormone therapy consisted of antiandrogen in 29 (40%), LHRH (luteinizing hormone-releasing hormone) agonist in eight (11%), and maximum androgen blockade in 36 (49%). Median duration of each neoadjuvant hormone therapy was 5 months, 13 months, and 8.5 months for antiandrogen, LHRH agonist, and maximum androgen blockade, respectively. Adjuvant hormone therapy was not performed in this series.

The TPI was performed exclusively with ^{125}I seeds (OncoSeed, MediPhysics, Kobe, Japan) of 0.394 mCi (14.6 MBq) or 0.385 mCi (14.2 MBq). About 3 weeks before the implant, prostate volumetry by axial transrectal ultrasound (TRUS; ProSound 4000, Aloka, Tokyo, Japan) with 5-mm intervals was performed with a Foley catheter in place. The TRUS was mounted on the stepper (AccuSeed, CMS, St. Louis, MO, USA). The prostate contour (= clinical tumor volume) was extracted and stored in VariSeed version 7.01 (Varian, Palo Alto, CA, USA) and 3-mm margins were placed around the clinical tumor volume to construct the planning target volume (PTV) in all directions except in the rectal direction, where no margin was added to reduce the rectal dose. In the preplanning, ^{125}I seeds were placed with the modified peripheral loading to deliver 145 Gy to the PTV. The TPI was performed under epidural anesthesia and ^{125}I seeds were implanted by Mick Applicator™ (Mick Radionuclear, Mount Vernon, NY, USA) through the appropriate template holes according to the preplanning with intraoperative modifications.

1 month after the TPI, final postplanning dosimetry was performed in all patients, because it has been reported that the prostate volume increases by trauma-associated fluid accumulation and bleeding within the gland immediately after the implantation [9, 13, 16]. A computed tomography (CT) image

Table 1. Patient characteristics. PSA: prostate-specific antigen.

Tabelle 1. Patientencharakteristik. PSA: prostataspezifisches Antigen.

	Patients n (%)
Age (years), median (range)	70.0 (48–82)
Stage	
• T1c	73 (70)
• T2a	12 (12)
• T2b	6 (6)
• T2c	10 (10)
• T3a	2 (2)
• T3b	1 (1)
Initial PSA (ng/ml), mean	12.2
• < 10	67 (64)
• 10–20	22 (21)
• > 20	15 (14)
Gleason Score	
• < 7	66 (63)
• 7	27 (26)
• > 7	11 (11)
Risk grouping	
• Low	36 (35)
• Intermediate	48 (46)
• High	20 (19)
Neoadjuvant hormone therapy	73 (70)
Follow-up (months), median (range)	13.0 (2–34)

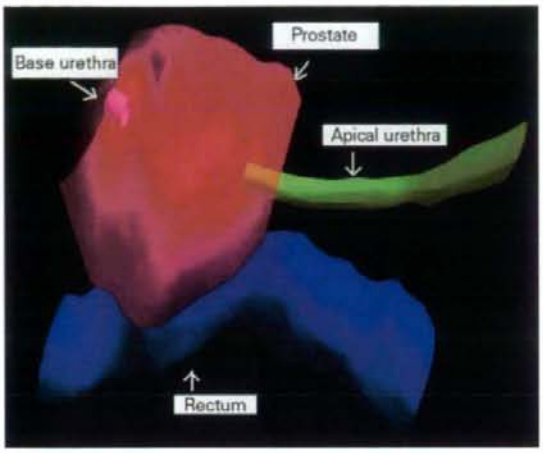

Figure 1. Definitions of base and apical urethras.

Abbildung 1. Definitionen der basalen und apikalen Urethra.

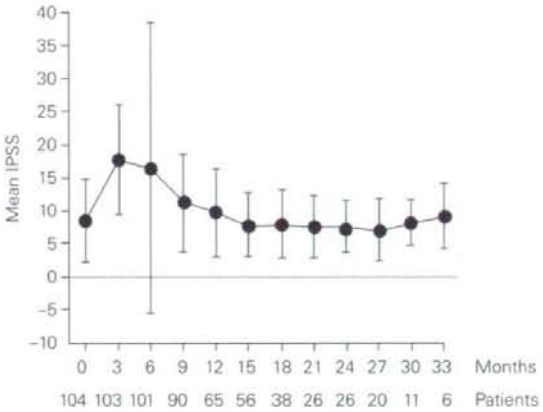

Figure 2. Change of mean International Prostate Symptom Scores (IPSS) after transperineal permanent interstitial implant (TPI). The figures shown in the lowest row represent the number of patients assessable. Error bars represent standard deviations.

Abbildung 2. Zeitliche Veränderung der durchschnittlichen International Prostate Symptom Scores (IPSS) nach transperinealer permanenter interstitieller Brachytherapie. Die Ziffern in der unteren Reihe entsprechen der auswertbaren Patientenzahl im jeweiligen Zeitintervall. Die Fehlerbalken zeigen die Standardabweichungen.

was taken with 2- or 3-mm intervals. T2-weighted magnetic resonance (MR) images were fused with the CT images to help extract the prostate contour. CT and MR images were obtained with a Foley catheter in place. Dose calculation was performed with the VariSeed™. The urethral dose was calculated at the outer rim of the Foley catheter from the bladder neck to the CT slice where the most caudally located seed can be found. In all patients, an α-blocker was prescribed from the day following TPI until subsidence of urinary symptoms.

The increment of IPSS was defined as the difference between the preimplant IPSS and the maximal IPSS after the implant. Postimplant IPSS was evaluated in the 1st and 4th weeks after the implant, and then every 2–3 months.

Various patient, tumor, and treatment factors as well as the TPI dosimetric factors were analyzed to find statistically significant relationships with the increment of IPSS. For calculation of the prostate volume, an MR image taken at the time of postplanning was used. D_{90} indicates the minimal dose covering 90% of the prostate expressed in Gray, V_{100} and V_{150} represent volume ratio of the prostate receiving at least 100% and 150% of the prescribed dose, respectively. The urethral D_{max} (maximal dose) and urethral D_{90} (minimal dose covering 90% of the entire prostatic urethra) were also calculated. In addition, base and apical urethras were extracted from the postplanning CT. The base urethra is defined as the most proximal 2–3 mm long portion of the prostatic urethra (actually, contouring two slices of CT images) neighboring the bladder neck (Figure 1). The apical urethra is apical 6 mm of the prostatic urethra. For the base and apical urethras, the D_{max}, D_{50} (minimal dose covering 50% of the corresponding structure), and D_{90} were calculated.

The relationships between clinical and treatment variables and the increment of IPSS were analyzed by univariate analysis. The continuous variables were dichotomized to give the lowest p-values in the t-test, where the increment of IPSS score was considered continuous. The variables with p-values < 0.05 were further analyzed in multivariate analysis by logistic regression models. In the multivariate analysis, the patients were dichotomized by the mean increment of IPSS into the larger and smaller increments, while the clinical and treatment variables were treated as continuous.

Results

The time course of mean IPSS change after TPI every 3 months is shown in Figure 2 with the respective number of patients. The IPSS reached its maximum 3 months after the implant and decreased gradually until 15 months. The increment of IPSS after the implant ranged from –9 to 31 with a mean of 10.7.

The mean IPSS before TPI was 8.5, and the number of seeds implanted ranged from 40 to 114 with a mean of 71.3 (Table 2). Total activity of the implanted seeds ranged from 15.4 to 45.9 mCi (0.57–1.70 GBq). The mean prostate volume evaluated in post-TPI MR images was 22.9 ml. Prostate V_{100} ranged from 51.9% to 99.8% of the prostate volume, and in 62 of the 104 patients the prostate V_{100} of $\geq 90\%$ was attained.

Table 2. Treatment and dosimetric characteristics. IPSS: International Prostate Symptom Score; SD: standard deviation; TPI: transperineal permanent interstitial implant. For detailed definitions of the dosimetric parameters refer to the text.

Tabelle 2. Therapeutische und dosimetrische Charakteristika. IPSS: International Prostate Symptom Score; SD: Standardabweichung; TPI: transperineale permanente interstitielle Brachytherapie. Genaue Definitionen der dosimetrischen Parameter finden sich im Text.

	Mean (SD)
Pre-TPI IPSS	8.5 (6.2)
IPSS increment	10.7 (6.9)
Prostate volume (ml)	22.9 (8.4)
Implanted seeds (n)	71.3 (13.6)
Seed activity (mCi)	28.2 (5.8)
Seed activity (GBq)	1.04 (0.21)
Prostate V_{100} (%)	89.5 (8.2)
Prostate V_{150} (%)	55.5 (14.3)
Prostate D_{90} (Gy)	147.2 (27.4)
Urethra D_{max} (Gy)	239.5 (55.7)
Urethra D_{90} (Gy)	100.5 (31.2)
Apical urethra D_{max} (Gy)	219.9 (43.2)
Apical urethra D_{90} (Gy)	100.8 (34.1)
Apical urethra D_{50} (Gy)	166.0 (36.5)
Base urethra D_{max} (Gy)	162.4 (43.3)
Base urethra D_{90} (Gy)	116.0 (31.7)
Base urethra D_{50} (Gy)	134.6 (34.5)

Table 3. Results of the univariate analysis to demonstrate the influence of clinical and dosimetric variables upon the increment of International Prostate Symptom Score (IPSS). PSA: prostate-specific antigen. For detailed definitions of the dosimetric parameters refer to the text.

Tabelle 3. Ergebnisse der univariaten Analyse, die den Einfluss der klinischen und dosimetrischen Varianten auf die Zunahme des International Prostate Symptom Score (IPSS) zeigen. PSA: prostataspezifisches Antigen. Genaue Definitionen der dosimetrischen Parameter finden sich im Text.

Variables		p-value
Age (years)	(≥ 73 years vs. < 73 years)	0.0039
PSA (ng/ml)	(≥ 20 ng/ml vs. < 20 ng/ml)	0.0100
Gleason Score	(≥ 7 vs. < 7)	0.67
Preimplant IPSS	(≥ 7 vs. < 7)	0.10
Prostate volume (ml)	(≥ 20 ml vs. < 20 ml)	< 0.0001
Implanted seeds (n)	(≥ 65 vs. < 65)	0.0017
Neoadjuvant hormone therapy	(+ vs. −)	0.0508
Prostate V_{100} (%)	(≥ 90% vs. < 90%)	0.0102
Prostate V_{150} (%)	(≥ 50% vs. < 50%)	0.0644
Prostate D_{90} (Gy)	(≥ 145 Gy vs. < 145 Gy)	0.0075
Urethra D_{max} (Gy)	(≥ 290 Gy vs. < 290 Gy)	0.5351
Urethra D_{90} (Gy)	(≥ 87 Gy vs. < 87 Gy)	0.1881
Apical urethra D_{max} (Gy)	(≥ 261 Gy vs. < 261 Gy)	0.4078
Apical urethra D_{90} (Gy)	(≥ 87 Gy vs. < 87 Gy)	0.3675
Apical urethra D_{50} (Gy)	(≥ 145 Gy vs. < 145 Gy)	0.5147
Base urethra D_{max} (Gy)	(≥ 188.5 Gy vs. < 188.5 Gy)	0.0003
Base urethra D_{90} (Gy)	(≥ 116 Gy vs. < 116 Gy)	0.0044
Base urethra D_{50} (Gy)	(≥ 116 Gy vs. < 116 Gy)	0.0015

Mean prostate D_{90} was 147.2 Gy with 61 patients showing the value ≥ 145 Gy. The urethral D_{max} was higher in the apical urethra as compared to the base urethra.

Univariate analysis of the various parameters and the increment of IPSS revealed that age, initial PSA, post-TPI prostatic volume, number of seeds implanted, prostate V_{100} and D_{90}, D_{max}, and D_{90} and D_{50} of the base urethra were statistically significantly related to the IPSS increment (Table 3). These parameters were further examined in a multivariate analysis, which demonstrated that the increment of IPSS correlated with the postimplant prostatic volume, number of implanted seeds, and the dosimetric parameters of the base urethra (Table 4). A higher dose to the base urethra caused a more unfavorable acute IPSS increment.

Discussion

As we experienced only one patient with acute urinary retention after TPI during this time period, we confined our analysis to the increment of IPSS as an acute urinary morbidity. Like other studies using ^{125}I, our study demonstrated that the IPSS increased maximally around 3 months after TPI and returned to the pretreatment level at about 12 months [2, 11]. There are several clinical as well as dosimetric parameters reported to correlate with the urinary morbidities after TPI. In the present study, the prostatic volume and the number of implanted seeds show a statistically significant relation to the increment of IPSS. Kelly et al. [7] and Bottomley et al. [3] also found an influence of prostatic volume and number of implanted seeds upon the increment of IPSS. Additionally, pretreatment IPSS [3, 7, 10], pretreatment urinary flow [19], number of needles used for seed implant [3, 8], and neoadjuvant hormone therapy [4] have been reported to be related to the increment of IPSS. Although it is rational to assume that urethral dose is related to the increment of IPSS, the relationship between them remains quite controversial. Our study revealed that the dosimetric parameters of the base urethra have a statistically significant impact upon the increment of IPSS. Similarly, Williams et al. found a relationship between increment of IPSS and the number of seeds above the prostatic base [19]. They consider the number of seeds above the prostatic base to reflect the dose to the bladder neck and trigone which may be sensitive to radiation. Pinkawa et al. suggested that the seminal vesicle dose is closely related to the dose to the bladder neck and the urethral sphincter muscle and late urinary dysfunction is more frequent in patients with a higher seminal vesicle dose [12]. By contrast, Allen et al. could not find sig-

Table 4. Results of the multivariate analysis to demonstrate the influence of clinical and treatment variables upon the increment of International Prostate Symptom Score (IPSS). MRI: magnetic resonance imaging; PSA: prostate-specific antigen. For detailed definitions of the dosimetric parameters refer to the text.

Tabelle 4. Ergebnisse der multivariaten Analyse, die den Einfluss der klinischen und dosimetrischen Varianten auf die Zunahme des International Prostate Symptom Score (IPSS) zeigen. MRI: Magnetresonanztomographie; PSA: prostataspezifisches Antigen. Genaue Definitionen der dosimetrischen Parameter finden sich im Text.

Variables	p-value
Age (years)	0.9033
PSA (ng/ml)	0.1901
MRI volume (ml)	0.0006
Seed	0.0151
Prostate V_{100} (Gy)	0.9123
Prostate D_{90} (Gy)	0.2841
Base urethra D_{max} (Gy)	0.0530
Base urethra D_{90} (Gy)	0.0151
Base urethra D_{50} (Gy)	0.0095

nificant relationships between various segmental urethral dose parameters and time to the resolution of IPSS increment, although they showed the maximal IPSS is related to the maximal apical urethral dose [1]. They segmented the prostatic urethra into base, midgland and apex each with 1 cm length, while our study limited base urethra only to the proximal 2–3 mm of prostatic urethra, which might have disclosed the sensitivity of this tiny region or bladder neck to radiation.

In this retrospective analysis, the patients included had been treated at the very initial phase after the introduction of TPI in our department. Therefore, in some patients the optimal quality of seed implantation was not attained and urethral dose reached < 100% of the prescribed dose. Although it is required to deliver an adequate dose to sterilize tumor cells around the base urethra, severity of the acute urinary morbidities represented by the increment of IPSS seems to be lowered by reducing the dose to the base urethra toward the prescribed dose.

Conclusion

The base urethra or bladder neck appears to be susceptible to radiation and the increased dose to this region acutely deteriorates IPSS. It remains unclear whether the radiation dose to this region relates to the incidence of late urinary morbidities.

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original article

Annals of Oncology 19: 49–55, 2008
doi:10.1093/annonc/mdm494
Published online 26 October 2007

Psychological and behavioral mechanisms influencing the use of complementary and alternative medicine (CAM) in cancer patients

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Received 8 May 2007; revised 6 September 2007; accepted 14 September 2007

Background: This study explored the psychological and behavioral mechanisms of complementary and alternative medicine (CAM) use in Japanese cancer patients using two applied behavioral models, the transtheoretical model (TTM), and theory of planned behavior (TPB).

Patients and methods: Questionnaires were distributed to 1100 patients at three cancer treatment facilities in Japan and data on 521 cancer patients were used in the final analysis. The questionnaire included items based on TTM and TPB variables, as well as three psychological batteries.

Results: According to the TTM, 88 patients (17%) were in precontemplation, 226 (43%) in contemplation, 33 (6%) in preparation, 71 (14%) in action, and 103 (20%) in maintenance. The model derived from structural equation modeling revealed that the stage of CAM use was significantly affected by the pros, cons, expectation from family, norms of medical staff, use of chemotherapy, period from diagnosis, and place of treatment. The primary factor for the stage of CAM use was the expectation from family.

Conclusions: The findings revealed the existence of a number of psychologically induced potential CAM users, and psychological variables including positive attitude for CAM use and perceived family expectation greatly influence CAM use in cancer patients.

Key words: CAM, cancer patients, psychological adjustment, theory of planned behavior, transtheoretical model

introduction

Cancer patients use nutritional supplements, psychological techniques, and natural medical approaches together with conventional medicine, or in replace of conventional therapy, which are so-called complementary and alternative medicine (CAM). Recent surveys have demonstrated the high prevalence of CAM use by cancer patients. Sixty-seven percent of Canadian respondents reported using CAM, most often in an attempt to boost the immune system [1]. The first national survey on the use of CAM in Japan revealed that 45% of Japanese cancer patients have used CAM [2].

CAM is defined by the National Center for Complementary and Alternative Medicine as 'a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine' [3] In addition, a new operational definition of CAM was proposed that it should include patients' perspectives, such as individual goals, objectives, and beliefs of the patients [4]. Therefore, it is important to consider psychological aspects such as patients' background, reasons or intentions for using CAM in oncology.

Several studies have explored the background and reasoning behind CAM use [1, 5–7]. CAM use in early-stage breast cancer patients was regarded as a marker of greater psychosocial distress and a worse quality of life [7] and advanced-stage cancer patients who used CAM had higher levels of anxiety and pain, lower satisfaction with conventional medicine, and a lower need for control over treatment decisions [8]. Alternatively, the use of CAM by cancer patients has not been associated with perceived distress or poor compliance with medical treatment [9]. However, the psychological and behavioral mechanisms of CAM use have not yet been clarified. Therefore, we carried out a multicenter cross-sectional survey to explore the psychological mechanism of CAM use in Japanese cancer patients from patients' perspectives, using the transtheoretical model (TTM), and the theory of planned behavior (TPB).

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The TTM [10] is useful for explaining changes in health behavior and has been used in various programs such as smoking cessation [11], genetic testing for colorectal cancer [12], and mammography adoption [13]. In the TTM, the decisional balance between pros and cons—positive and negative attitudes for the behavior—will account for the state of change observed during five stages: precontemplation, contemplation, preparation, action, and maintenance [10]. We adopted this classification to explain the behavioral intention of patients using CAM in cancer treatment. Moreover, self-efficacy, which acts as a mediating function for the psychological adjustment of cancer patients [14, 15], is an important factor affecting a person's movement from one stage to another.

The TPB [16] examines behavioral intentions based on three major components: the patient's attitude towards the behavior, perceived control, and subjective norms. In cases of cancer patients, attitude towards behavior may include perceived effectiveness of treatment, anxiety regarding side-effects, etc. Perceived control is the individual's perception of the extent to which performance of the behavior is easy or difficult, and is synonymous with the concept of self-efficacy [16]. Subjective norms in cancer CAM include expectation from family members, and norms of medical staff towards the patients.

Our hypotheses are as follows: (i) cancer patients are classified into five stages of CAM use, (ii) the stage of CAM use is explained by TTM and TPB variables, and (iii) perceived control positively correlates with CAM use and mediates between CAM use and psychological adjustment.

patients and methods

participants

This study was approved by the institutional review boards of the Kinki Chuo Chest Disease Center, National Kyushu Cancer Center, and National Shikoku Cancer Center. From April 2005 to August 2005, a total of 1100 questionnaires were distributed to patients at each institute. Patients were enrolled in the study after their attending physician assessed if they met the following conditions: were receiving medical treatment through the outpatient or inpatient units at any of the three cancer centers, had an Eastern Cooperative Oncology Group performance status [17] from zero to three, were physically able to fill in the questionnaires by themselves, and had no cognitive impairment. On the questionnaire, we explained the purpose of the study and the fact that returning the questionnaire would be regarded as consent for participation; though we asked the patients to return the questionnaires anonymously.

measures

For this study, we developed our own questionnaire to examine CAM use in cancer patients (available from the authors). The questionnaire contained 85 items and it took about 20 min to complete. On the cover page of the questionnaire, CAM was defined using same definition of our previous survey [2]: 'as any therapy is not included in the orthodox biomedical framework of care for patients, which includes remedies used without the approval of the relevant government authorities of new drugs after peer review of preclinical experiments and clinical trials regulated by law. Health insurance does not usually cover the cost of CAM, and patients are generally liable for all expenses incurred by CAM use. CAM may include use of natural products from mushrooms, herbs, green tea, shark cartilage, megavitamins, or other special foods, and may incorporate acupuncture, aromatherapy, massage, meditation, etc'. Additionally, a sheet containing 20 examples of CAM therapies and products was attached to the questionnaire. The first portion of the questionnaire asked for information on the patients' background, including type of disease, age at onset, current age, gender, educational level, economic status, type of cancer treatment, satisfaction with treatment, smoking, drinking, and social support measured by the single item Tangible Social Support Scale [18].

The second part of the questionnaire included items originally designed to evaluate the cancer CAM-specific TTM and TPB variables. To measure the patients' subjective intention with regard to CAM use, we additionally defined cancer CAM use as those 'using any supplements or dietary foods or receiving any therapy that appears to have anticancer effects or auxiliary effect to that of conventional cancer therapy'. Respondents were asked to rate themselves based on the five stages of the TTM [10]: precontemplation ("I have no interest in using CAM"), contemplation ("I have been thinking that I might want to use CAM"), preparation ("I am preparing to use CAM"), action ("I have already used CAM in the last 6 months"), and maintenance ("I have already used CAM for >6 months"). The next section was composed of 27 items measuring TTM and TPB variables. The items were measured on a five-point Likert-type scale that ranged from 'not at all' (1) to 'extremely' (5). They included following five categories, (i) positive attitudes for CAM; (ii) pros; (iii) cons; (iv) expectation from family; and (v) norms of medical staff. The items were developed in our previous study on CAM [2] and another study on dietary food intake [19]. We used 16 from 27 items using confirmatory factor analysis on the current data as structurally valid and reliable items (Table 1). Also, content validity of the all TTM and TPB items in this part was confirmed by experts of two physicians, one psychiatrist and two psychologists.

To assess psychological adjustment, we used the Japanese version [20] of the Hospital Anxiety and Depression Scale (HADS) [21], which has 14 questions on anxiety and depression with each question rated from 0 to 3. The validity and reliability of the Japanese HADS in cancer patients has been confirmed previously [22].

To assess perceived control in patients, we used the Self-Efficacy for Advanced Cancer (SEAC) scale, which was designed to evaluate self-efficacy of cancer patients [23]. The SEAC scale has 18 items with three subscales: symptom coping efficacy, activities of daily living efficacy (ADE), and affect regulation efficacy (ARE). The scale was formatted on an 11-point Likert-type scale ranging from 0 (not at all confident) to 100 (totally confident). The reliability and validity of this scale were also confirmed [23].

Finally, the Japanese version of the MD Anderson Symptom Inventory (MDASI-J) [24] was developed as a brief multiple-symptom assessment scale. It consisted of 13 symptom items [25], and its validity and reliability were confirmed [24]. We used 10 of the 13 physical symptom items for our statistical analyses since the items for distress, sadness, and remembrance were significantly and highly correlated with the HADS total score ($r = 0.0479$, $P < 0.001$; $r = 0.456$, $P < 0.001$; $r = 0.334$, $P < 0.001$, respectively).

statistical analyses

Descriptive analyses were carried out summarizing the participants' backgrounds and scores following psychological measurements. Those with >30% missing values on the questionnaire were excluded from the analyses. The factors predicting stage of CAM use were analyzed through univariate analysis using the analysis of variance. In order to carry out multivariate analyses, we transformed the participants' responses for the stage of CAM use into a numeric scale ranging from 1 to 5 points (1, precontemplation; 2, contemplation; 3, preparation; 4, action; and 5, maintenance), according to a previous study [15]. Next, structural equation modeling (SEM) using the maximum likelihood method was carried out to

Table 1. Items measuring TTM and TPB variables and factor definitions

Items	Factor loadings
Positive attitudes for CAM (Cronbach alpha = 0.83)	
Definition: The items represented the high-perceived availability and importance of CAM use for the patients.	
1. CAM is important to retain physical strength.	0.80
2. Hospital care alone is not enough.	0.68
3. Convenience is an important determinant of starting to use CAM.	0.84
4. The cost of CAM is important.	0.66
Pros (Cronbach alpha = 0.90)	
Definition: The items represeinted patients' perceived positive outcomes of CAM use.	
5. The use of CAM leads to the cure of disease.	0.90
6. The use of CAM halts the progression of disease.	0.89
7. The use of CAM boosts physical and immune strength.	0.90
8. CAM has fewer side-effects compared with medical care.	0.69
Cons (Cronbach alpha = 0.70)	
Definition: The items represented patients' perceived negative outcomes of CAM use.	
9. The use of CAM has bad influence on medical care.	0.79
10. The use of CAM deteriorates disease.	0.89
11. I am aware of the side-effects of CAM.	0.53
12. I am aware of the dependence liability of CAM.	0.53
Expectation from family (Cronbach alpha = 0.65)	
Definition: The items represented patients' perceived expectations and recommendations from family.	
13. My family/friends believe that I should be actively engaged in the use of CAM.	0.74
14. My use of CAM is influenced by the opinions of my family/friends.	0.65
Norms of medical staff (Cronbach alpha = 0.34)	
Definition: The items represented patients' perceived expectation, recommendation from patients' medical staff, or their norms.	
15. My doctors/nurses believe that I should be actively engaged in the use of CAM.	0.68
16. My use of CAM is influenced by the opinions of my doctors/nurses.	0.30

Fit indices from the confirmatory factor analysis for items and factors indicated above: chi-square (96) = 345.5; $P = 0.001$; GFI = 0.92; AGFI = 0.88; CFI = 0.94; RMSEA = 0.07.
TTM, transtheoretical model; TPB, theory of planned behaviour; CAM, complementary and alternative medicine.

test the model. Because the model needed a parsimonious structure, we used the mean scores of SEAC as 'self-efficacy', the total score of HADS as 'psychological distress', and the mean scores of 10 items of MDASI-J as 'physical sympotom'. We conducted all statistical analyses using SPSS (version 14.0) and AMOS (version 5.0.1) software packages.

results

response rate to questionnaire

Of the 1100 questionnaires, 750 were given to inpatients and 350 to outpatients. Out of the 651 questionnaires returned (response rate 59.2%), 521 were valid for statistical analyses. The rest ($n = 130$) were invalid because of the lack of major information such as disease name or stage of CAM use. Moreover, questionnaires from noncancer patients were excluded from the analyses. Thus, the rate of valid replies was 47.4%.

backgrounds of patients and distribution of CAM use

The participants consisted of 246 males and 270 females, and five unknowns. Table 2 summarizes the demographic and diagnostic information of the participants. For staging, 88 patients (16.9%) were in precontemplation, 226 (43.4%) in contemplation, and 31 (6.6%) in preparation among the 347 CAM nonusers (66.6%), with 71 (13.6%) in action and 103 (19.8%) in maintenance among the 174 CAM users (33.4%). Table 1 also shows the prevalence of the five stages of CAM use categorized by demographic and medical status variables. The prevalence of CAM use in the higher stages, including action and maintenance, was significantly higher in patients who received chemotherapy ($P < 0.001$), those dissatisfied with current conventional treatment ($P < 0.05$), and outpatients ($P < 0.001$).

psychosocial factors associated with the stages of CAM use

Table 3 shows the mean response and the results of the univariate analyses for psychological variables, physical symptom variables, and social support obtained from patients at each of the five stages of CAM use. There were significant differences amongst patients in the five stages based on pros ($P < 0.001$), cons ($P < 0.001$), positive attitude for CAM ($P < 0.001$), and expectation from family members ($P < 0.001$). There was a slightly higher response on ADE ($P < 0.10$) in patients who were in the action and maintenance stages.

structural model for stages of CAM use

We carried out SEM by first selecting 14 variables in the initial model because they were observed to be significant predictors in the univariate analysis or were essential components for the TTM and TPB theories: use of chemotherapy, period from diagnosis, whether need for treatment was met, treatment place, stage of CAM use, psychological distress, pros, cons, positive attitude, expectation from family members, norms of medical staff, self-efficacy, psychological distress, physical symptoms, and social support. Next, we drew all paths according to the results of the correlation analysis. Since there was a significantly strong correlation between the pros and a positive attitude ($r = 0.80$, $P < 0.001$), and since the explanation by the TTM is given a priority for our purposes, we dropped positive attitude from the initial model. We repeated the SEM and sequentially dropped paths that were not significant until all the paths in the model became significant ($P < 0.05$). The variable 'met need for treatment' was dropped from the model because all the paths from this variable became not significant.

Figure 1 represents the final model. The fit indices for this model were excellent and included the following: chi-square

Table 2. Patients' background and CAM use stage

	Total	Precontemplation		Contemplation		Preparation		Action		Maintenance		P (χ^2 test)
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Total	521	88	16.9	226	43.4	33	6.3	71	13.6	103	19.8	
Age years												
>60	262	47	17.9	120	45.8	13	5.0	31	11.8	51	19.5	0.446
≤60	253	40	15.8	105	41.5	19	7.5	40	15.8	49	19.4	
Gender												
Male	270	43	15.9	112	41.5	22	8.1	35	13.0	58	21.5	0.336
Female	246	45	18.3	110	44.7	11	4.5	36	14.6	44	17.9	
Education												
High school	318	50	15.7	141	44.3	7.2	7.2	46	14.5	58	18.2	0.561
Posthigh school	174	34	19.5	67	38.5	10	5.7	25	14.4	38	18.2	
Period from diagnosis												
≤1 year	261	56	21.5	118	45.2	20	7.7	46	17.6	21	8.0	0.000
>1 year	246	29	11.8	102	41.5	10	4.1	25	10.2	80	32.5	
Conventional treatment												
Chemotherapy	393	58	14.8	158	40.2	28	7.1	61	15.5	88	22.4	0.001
Nonchemotherapy	122	27	22.1	66	54.1	5	4.1	10	8.2	14	11.5	
Treatment met patient's needs												
Yes	371	72	19.4	161	43.4	18	4.9	49	13.2	71	19.1	0.045
No	150	16	10.7	65	43.3	15	10.0	22	14.7	32	21.3	
House income												
≥¥7 000 000	113	17	15.0	48	42.5	5	4.4	13	11.5	30	26.5	0.438
<¥7 000 000	334	53	15.9	144	43.1	23	6.9	50	15.0	64	19.2	
Treatment place												
Inpatient ward	360	67	18.6	167	46.4	27	7.5	53	14.7	46	12.8	0.000
Palliative care unit	24	2	8.3	8	33.3	5	20.8	3	12.5	6	25.0	
Outpatient clinic	161	21	13.0	59	36.6	6	3.7	18	11.2	57	35.4	
Cancer												
Lung	190	28	14.7	69	36.3	11	5.8	34	17.9	48	25.3	0.137
Breast	55	11	20.0	30	54.5	4	7.3	4	7.3	6	10.9	
Gastrointestinal	79	13	16.5	40	50.6	6	7.6	10	12.7	10	12.7	
Gynecological	61	8	13.1	28	45.9	2	3.3	7	11.5	16	26.2	
Other	121	24	19.8	54	44.6	9	7.4	13	10.7	21	17.4	

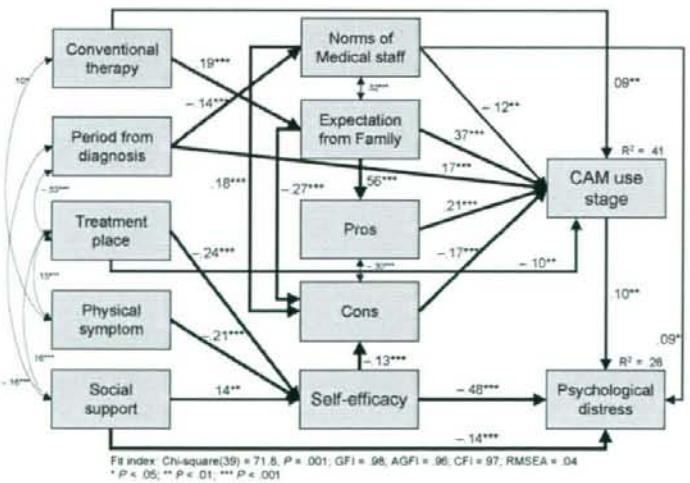

Figure 1. Structural model for the stage of CAM use and psychological adjustment.