(図2－2).

2.　味覚障害の比較

味覚障害に対するCepharanthinの効果を全口腔法による味覚検査にて比較検討した（図3）．治療終了直後までは4基本味のすべてにおいて両群ともに認知閾値の上昇を認めたが，治療終了後6カ月の時点ではすべての味覚の回復を認めた．甘味は30Gy照射時に，また塩味では30Gy照射時と治療終了直後において，対照群に比べCepharanthin投与群では有意に閾値の上昇が少なく，甘味と塩味に関する味覚障害がCepharanthin投与群では軽減されていた．

3.　自覚症状の比較

アンケート結果に基づき自覚的な唾液の性状について比較したところ，両群間に明らかな差は認めなかった．両群ともに60%以上の症例が30Gy照射の時点で既に唾液分泌量の低下を自覚しており，治療終了6カ月後においても60%以上の症例で回復は認められなかった(図4－1)．

また両群ともに60%以上の症例で30Gy照射時に自覚的な味覚の低下を認め，治療終了後6カ月でも50%以上の症例で障害が残存していた．ただし，Cepharanthin投与群では，治療中および治療後における味覚脱失症例

表2　全口腔法検査溶液の濃度

濃度番号	甘味 ショ糖	塩味 食塩	酸味 クエン酸	苦味 塩酸キニーネ
1	10 (3.420)	10 (0.5844)	0.32 (0.06724)	0.01 (0.003609)
2	32 (10.944)	32 (1.8701)	1 (0.210140)	0.032 (0.0155488)
3	100 (34.200)	100 (5.8440)	3.2 (0.672448)	0.1 (0.03609)
4	320 (109.440)	320 (18.7008)	10 (2.10140)	0.32 (0.115488)
5	1000 (342.000)	1000 (58.440)	32 (6.72448)	1 (0.3609)

mM（g/l）

表3　自覚症状アンケートの内容

唾液について	(1) 自覚的に正常である． (2) 唾液の量は減ったが，性状に変化はない． (3) 唾液の量が減り，粘調になった． (4) 唾液がほとんど出ない．
味覚について	(1) 味覚は正常である． (2) 軽度味覚障害を自覚（少し味が薄くなった．） (3) ほとんどあるいは全く味覚がない．
口腔内不快感について	(1) 不快感はない． (2) 軽度の不快感はあるが，ほとんど気にならない． (3) 重度の不快感を常時自覚する． (4) 不快感とともに咽頭痛を自覚する．

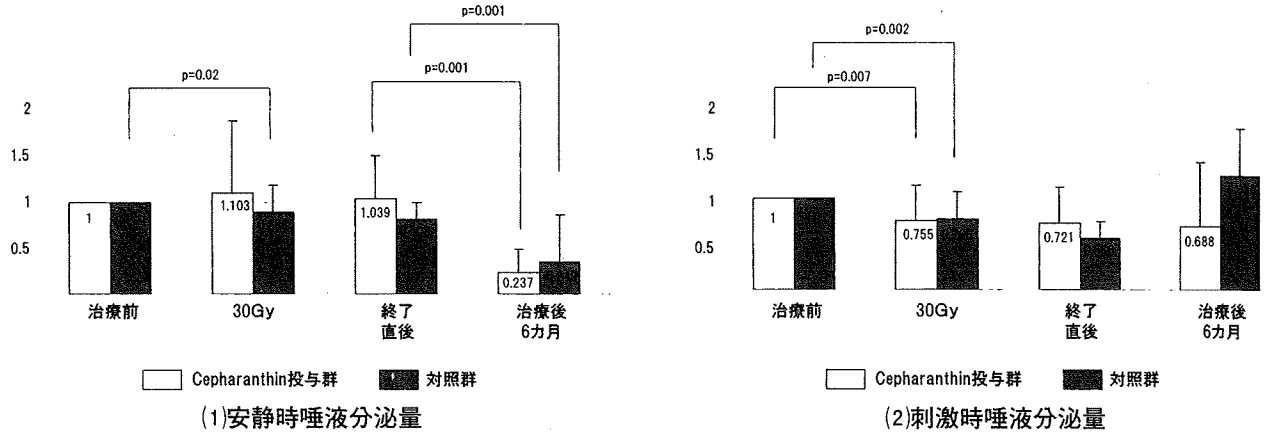

図2　唾液分泌量の比較

治療前の唾液分泌量を1とし，それに対する分泌量の比率を示す．

(1) 安静時唾液分泌量：対照群では治療前と30Gy照射時の分泌量に有意差を認めるが，Cepharanthin投与群では治療後6カ月の時点まで有意な低下は認めない．

(2) 刺激時唾液分泌量：両群ともに治療前と比較して30Gy照射時には有意な低下を認める．

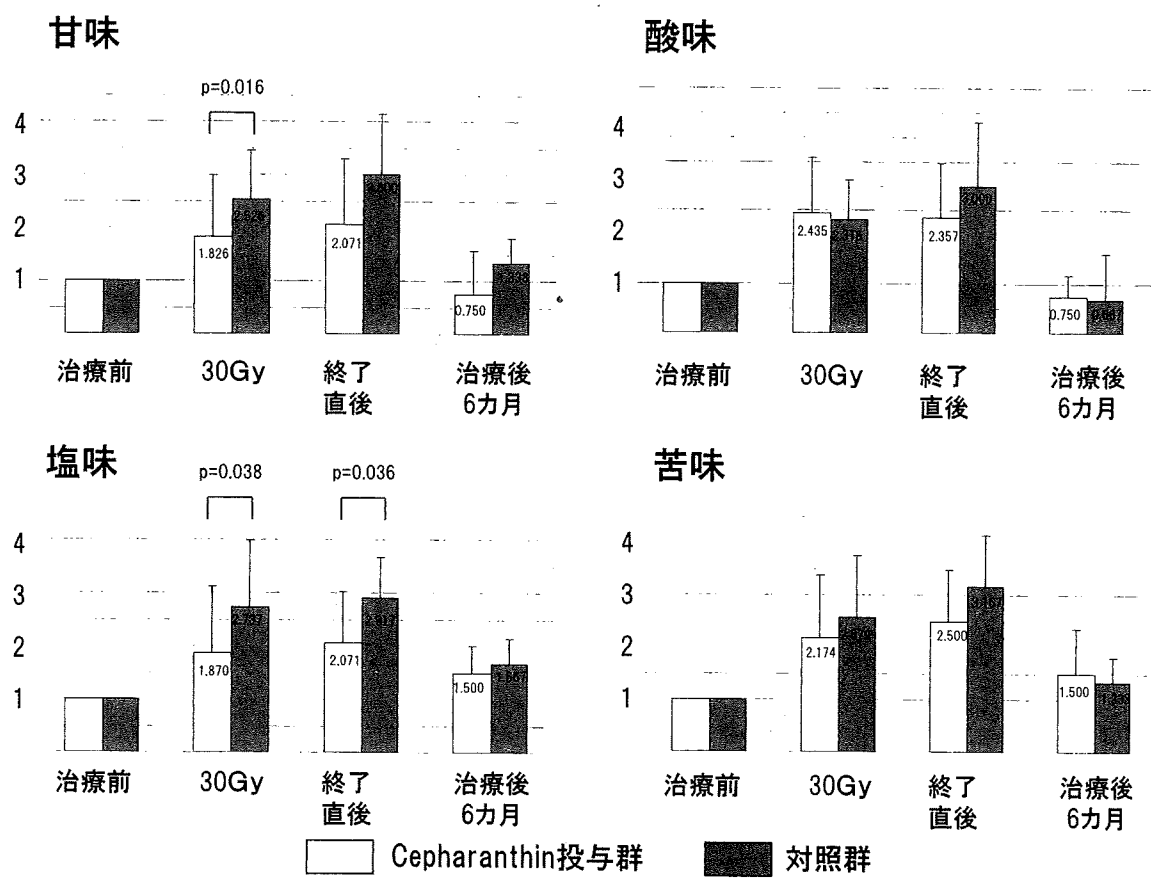

図3　味覚検査
4つの基本味質別に両群間で閾値の変動を比較した．治療前の認知閾値を1として，その後の閾値の変化率を示す．
甘味および塩味にてCepharanthin投与群と対照群間に有意差を認める．

が20%以下であり，対照群に比べ少ない結果であった（図4－2）．

口腔内不快感についても同様に30Gy照射時点で70%以上の症例に不快感がみられた．2群間を比較するとCepharanthin投与群では治療終了直後において重度不快感と咽頭痛を自覚する症例が50%であり対照群の76%に比べ少なく，治療終了6カ月後には全例で不快感の消失を認めた．これに対し対照群では，治療終了6カ月後においても半数の症例に不快感の残存を認めたが，両群間に統計学的有意差は認めなかった（図4－3）．

考　　察

Cepharanthinはツヅラフジ科植物タマサキツヅラフジの根茎から抽出精製したビスコクラウリン型アルカロイドを含有する製剤であり，さまざまな生物活性がみられ，これまで造血機能における放射線防護作用が報告されている[7][8][9]．頭頸部癌における放射線治療に対しても口腔粘膜炎の発生時期に対する遅延効果や口腔内乾燥症を軽減させる効果が報告されている[1][2]．そこで本研究においてわれわれは，頭頸部癌治療にて生じる放射線性唾液腺・味覚障害におけるCepharanthinの効果を定量的に評価することを目的とし，唾液分泌量の測定と味覚検査を行った．

まず唾液分泌量の比較であるが，安静時および刺激時において両群間に有意差は認めなかった．また刺激時唾液分泌量と自覚症状アンケートの唾液の性状においても両群間の差は認めなかった．しかし安静時唾液分泌量では，対照群において治療中には唾液分泌量の有意な低下を認めるが，Cepharanthin投与群では治療終了6カ月になるまで有意な低下を認めなかった．これはCepharanthinの放射線防護作用の可能性があると考える．唾液分泌量の低下は放射線治療開始早期より出現し，発現時期は10～20Gyとの報告がある[10]．さらに60Gyの根治線量を照射した場合，唾液腺組織では腺細胞の崩壊や間質結合織の増加といった著明な退行性変化が生じてくるため，不可逆的で永続的な唾液分泌障害を

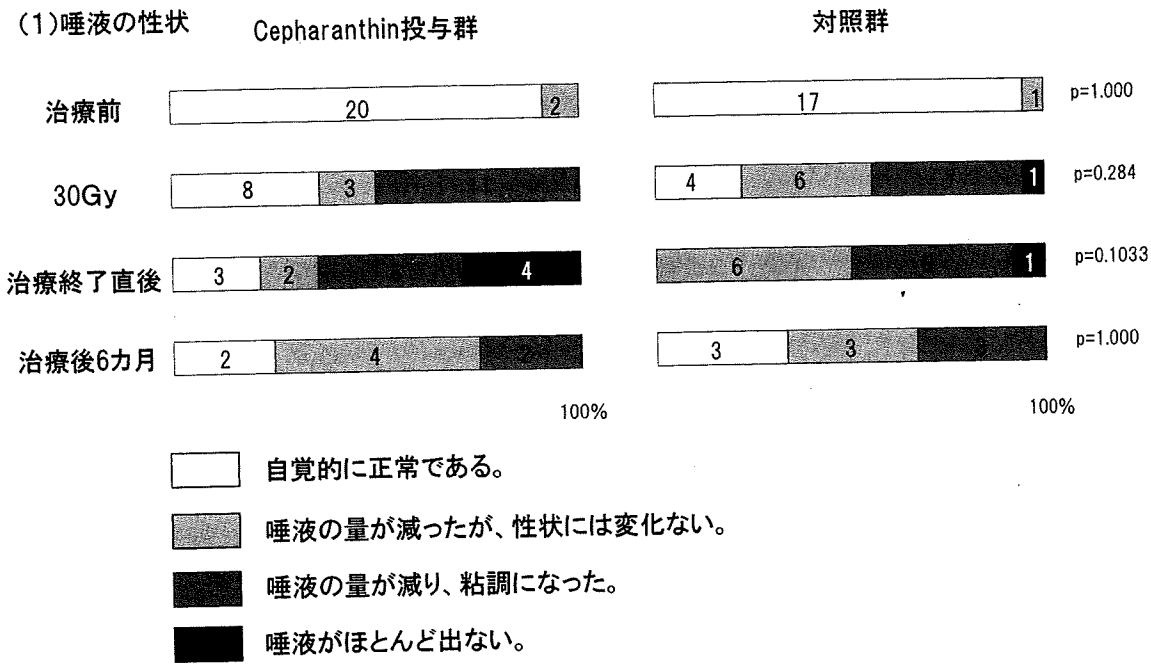

図4－1

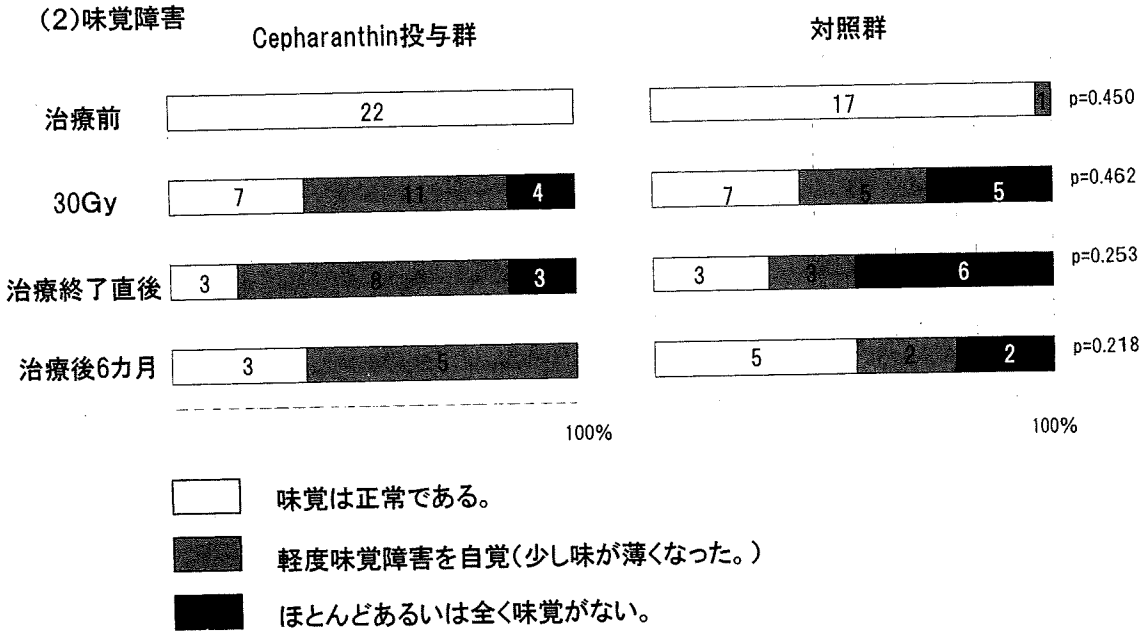

図4－2

受けるとされている[11]．今回の検討では30Gy照射時点から終了直後まで saxon 法を用いた刺激時唾液分泌量が著しく低下していたが，これに比べ安静時の分泌量の低下は軽度であった．一方，治療後6カ月時点では Cepharanthin 投与にかかわらず，安静時唾液分泌量は低下していたが，刺激時の分泌量は治療中の分泌量と変化がなかった．唾液腺の腺細胞には漿液腺と粘液腺があるが，漿液細胞は粘液細胞より放射線感受性が高く，そのため照射開始早期より変性が認められる[12]．安静時唾液分泌は漿液と粘液がバランスよく分泌されるが，刺激時には漿液性唾液が多量に分泌される[13]．今回，刺激時唾液分泌が照射早期より低下したのはこのためであると考えられる．また60Gy以上の根治照射を施行した唾液腺では，漿液腺と粘液腺ともに不可逆性の変性が生じるため安静時および刺激時唾液分泌ともに治療後長期間にわたって低下すると考えられる．

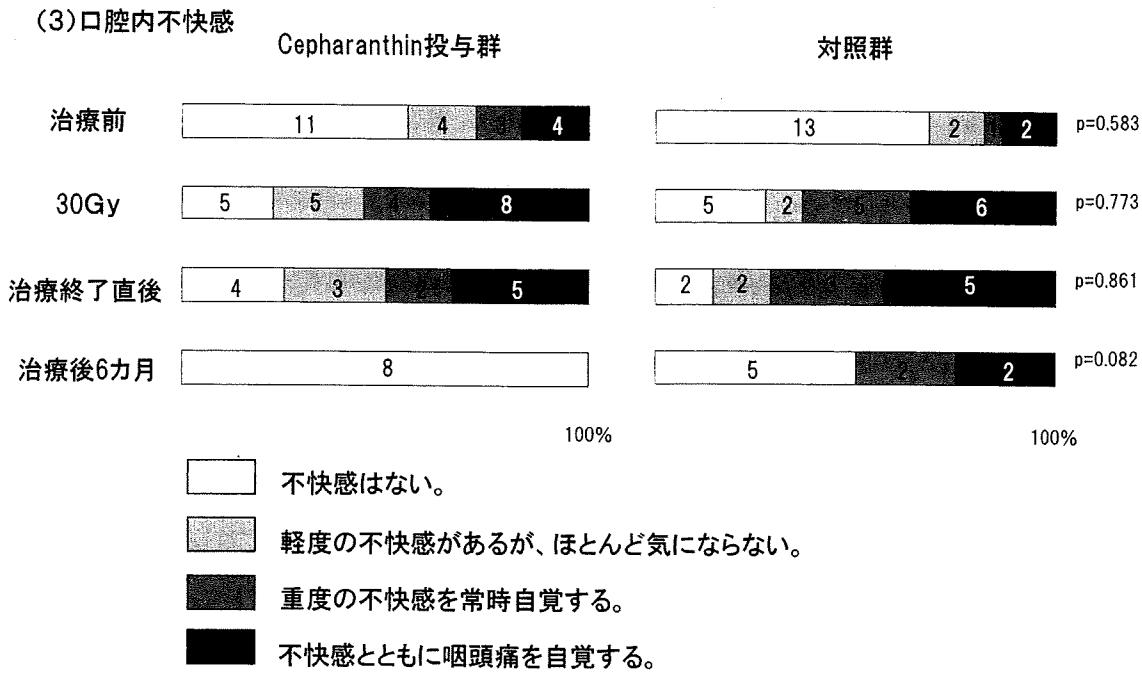

図4－3

図4　自覚症状アンケート結果（※グラフ内の数字は症例数を示す.）
自覚アンケートの結果について両群間で比較した．グラフ右にp値を示す.
各アンケート結果において有意差は認めない.

放射線性味覚障害の発生機序は，照射により味細胞が直接に傷害される感覚性障害，味求心性神経の神経経路での傷害である末梢神経障害，唾液分泌量の低下による伝導性障害，味蕾や末梢神経の栄養血管の侵襲による循環不全などが原因である[14]．今回の全口腔法による味覚閾値の定量的評価では，Cepharanthin投与により照射中の味覚障害を緩和できることが示され，特に甘味および塩味においては統計学的有意差を認めた．また自覚症状においてはCepharanthin投与群で味覚脱失例の頻度が少なくなる傾向がみられ，Cepharanthinに放射線性味覚障害を軽減する一定の効果があったと評価できる．なお今回，甘味と塩味にてCepharanthinの効果を認めたが，基本味質別の放射線障害については甘味が最も遅く障害が発現し，障害の程度も軽いとされている[14][15][16]．また今回の検討と同様に甘味や塩味の味覚低下の程度が酸味や苦味の味質と比較して比較的軽く，回復も早かったとの報告がある[17]．甘味は元来，糖質の味覚であって，生体のエネルギーとなる物質の味覚であるために，4味質の中で最も障害に対する抵抗性が高い[18]と考えられており，今回も味覚障害の程度が比較的軽度であったためCepharanthinの放射線防護作用が発揮されたのではないかと考えられた．

放射線性味覚障害は照射終了後60～120日で回復するといわれており[19]，今回の結果でも治療後6カ月の時点では両群ともに全口腔法による味覚閾値は治療前とほぼ同じレベルまで回復していたが，治療中は味覚閾値の上昇を全症例で認めた．頭頸部癌の化学放射線治療では，ほとんどの症例で抗癌剤の副作用である消化器症状に加え，放射線性味覚障害による摂食障害が生じ，血中蛋白質の低下や電解質異常などの全身状態の悪化が大きな問題となる．Cepharanthinは放射線性味覚障害を軽減する効果を持つことから，栄養摂取の面からも化学放射線治療中の全身状態の維持に有用な薬剤であると言える．

またCepharanthin投与群においては，統計学的有意差はみられなかったが，口腔内不快感を軽減できる傾向を認めた．これはCepharanthinの持つ口腔粘膜炎発症を抑制する効果[2]と密接な関連があると考えられ，治療後6カ月では，Cepharanthin投与群の全例で不快感がみられなかった．口腔内不快感は頭頸部癌，とりわけ咽頭癌および口腔癌において，治療後長期間にわたり患者の精神的苦痛の一因となるが，Cepharanthinは口腔内不快感においても患者のQOLを向上させる効果が期待できよう．

Cepharanthinは投与量に比例して高い効果が得られるとともに，副作用の出現もなく，安全性が高い[20]．また経口投与では腸管吸収にて90％が失われるが，経静脈

投与は経口投与と比較して吸収が圧倒的に速やかであり[21]，高い血中濃度を得ることができる．実際に前立腺癌の放射線治療におけるCepharanthinの正常組織防護効果は経口投与より経静脈投与が有効であったと報告されている[22]．頭頸部放射線治療における従来の報告ではCepharanthinを1日30mg経口投与している[1]が，本研究ではより高い効果を期待して30mgを週2回経静脈投与し，化学放射線治療中の唾液分泌障害や味覚障害の軽減効果が認められた．しかし投与量および投与期間については，更なる検討が必要であると考える．

Cepharanthinの作用機序として，サイトカイン産生促進作用，生体膜安定化作用，抗アレルギー作用，脂質過酸化反応抑制作用，血液幹細胞増加作用，副腎皮質ホルモン産生増加作用，末梢循環改善作用が報告されている[22]．化学放射線療法が施行された口腔内において，Cepharanthinの持つ複合的組織修復機構が作用した結果，サイトカインの増幅による味蕾および末梢神経細胞における放射線性障害の回復促進や，循環不全の抑制ならびに副腎皮質ホルモン産生増加による口腔粘膜炎症の抑制などの機序により，放射線性味覚障害の軽減が生じたと推察されるが，これについても今後の検討が必要である．

ま と め

頭頸部悪性腫瘍患者における放射線性唾液腺障害と味覚障害に対するCepharanthin効果について検討した．

1. Cepharanthinは化学放射線治療中の安静時唾液分泌量の低下を抑制する傾向を認めた．

2. Cepharanthinは放射線性味覚障害を軽減し，特に治療中の甘味および塩味において味覚閾値上昇の抑制効果を認めた．

3. Cepharanthinは自覚症状においても味覚脱失や口腔内不快感を抑制させる傾向を認めた．

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本論文の要旨は第107回日本耳鼻咽喉科学会総会・学術講演会（2006年，東京）において口演した．

（2008年10月10日受稿　2009年3月19日受理）

別刷請求先　〒849-8501 佐賀市鍋島5－1－1
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Cepharanthin Effect on Radiation-Induced Xerostomia and Taste Disorder in Patients with Head and Neck Cancer

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In evaluating the effect of cepharanthin on xerostomia and taste disorder in 40 patients undergoing radiotherapy for head and neck cancer, we administered cepharanthin intravenously during chemoradiotherapy to 22 patients, with 18 others as a control group. Cepharanthin did not significantly affect salivary secretion during and after chemoradiotherapy, although taste disorder and oral discomfort were alleviated. Cepharanthin may thus be effective in maintaining the quality of life of patients with head and neck cancer.

Keywords: cepharanthin, head and neck cancer, radiotherapy, xerostomia, taste disorder

Nippon Jibiinkoka Gakkai Kaiho (Tokyo) 112：648-655, 2009

Jpn J Clin Oncol 2007;37(9)641–646
doi:10.1093/jjco/hym101

Original Articles

A phase I–II Study of Bi-weekly Docetaxel Combined with Radiation Therapy for Patients with Cancer of the Larynx/hypopharynx

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Received January 13, 2007; accepted May 21, 2007

Background: We performed a phase I/IIstudy of bi-weekly docetaxel in combination with concurrent radiotherapy to enhance the cytotoxic effect and radiosensitization and improve the rate of laryngeal preservation.
Methods: Patients with T2N0-1M0, T3N0M0 hypopharyngeal cancer or T2N0-1M0, T3N0-1M0 larynx cancer were enrolled. Docetaxel was administered bi-weekly (days 1, 15, 29) from the first day of radiotherapy, while 2 Gy/day of radiation was given on 5 days weekly from day 1, reaching a total of 60 Gy in 30 fractions.
Results: 12 patients took part in the phase I study. The maximum tolerated dose (MTD) was 40 mg/m^2 and the recommended dose (RD) was determined as 35 mg/m^2. The phase II study was conducted with docetaxel at 35 mg/m^2 for 25 patients. Treatment was completed without interruption in 24 patients, with a protocol implementation rate of 96%. The complete response rate was 100% in laryngeal cancer, and 80% in hypopharyngeal cancer, and total (including partial response) overall response rate was 100%. The laryngeal preservation rate was 96%, and the overall local control rate was 92%. All patients have been alive for at least 3 years without any recurrence.
Conclusions: The chemoradiation therapy using bi-weekly docetaxel is an extremely effective treatment for cancer of the larynx/hypopharynx, provided that it is used for the specified stage of cancer.

Key words: larynx cancer – hypopharyngeal cancer – chemoradiation – docetaxel – laryngeal preservation

INTRODUCTION

Concurrent chemoradiotherapy for head and neck cancer confers a survival benefit (1), and therefor the regimen of cisplatin (CDDP) and 5-fluorouracil (5-FU) with radiation is widely used. However, some patients with renal complications can tolerate only limited treatment. Docetaxel (DOC) is an antineoplastic taxoid obtained by partial chemical modification of a splenocytotoxic precursor (10-docetyl baccatin III) extracted from the needles of the European yew tree. It stabilizes microtubules and elicits hyperplasia of microtubular bundles by promoting polymerization and also by inhibiting depolymerization of the microtubular proteins, thereby blocking cell division in the M phase (2). Since these cells are synchronized in the G2/M phase that is most sensitive to radiation, DOC has a strong radiosensitizing potential (3,4). In a phase I study of weekly DOC combined with radiation in Japan, the dose-limiting factor was mucositis, and the recommended dose was 10 mg/m^2(5). However, the dose intensity of weekly administration (10 mg/mg/m^2,

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i.e. 40 mg/m^2/month) seems insufficient to enhance the cytotoxic effect, and is just enough for a radiosensitization effect only. On the other hand, bi-weekly DOC administration enabled an increase in the dose. Furthermore bi-weekly DOC was found to be more convenient and tolerable than weekly DOC for breast cancer (6).

To improve the rate of laryngeal preservation, we investigated whether a bi-weekly bolus administration would produce enhanced cytotoxic effects, in addition to radiosensitization, and sought to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and the recommended dose (RD) in combined DOC and radiation therapy. Using the RD and the same protocol, we then conducted the phase II study.

PATIENTS AND METHODS

Patient Eligibility

The study population consisted of patients with T2N0-1M0, T3N0M0 hypopharyngeal cancer or T2N0-1M0, T3N0-1M0 laryngeal cancer, who met the protocol conditions. Inclusion criteria specified that patients should be aged 20–75 years and have a definitive pathological diagnosis of cancer of the head and neck, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, no previous radiotherapy, lesion(s) evaluated by imaging, provided informed consent and a life expectancy of at least 3 months. If the patients had previously received treatment, there had to be a minimum period of 1 month since the last treatment. Adequate hematological function (white blood cell count $\geq$4000/mm^3, neutrophil count $\geq$2000/mm^3, platelet count $\geq$100000/mm^3 and hemoglobin level $\geq$9.5 g/dl). Adequate hepatic function (aspartate aminotransferase and alanine aminotransferase $\leq$1.5 times the normal upper limit, total bilirubin $\leq$1.5 mg/dl and alkaline phosphatase $\leq$2.5 times the normal upper limit), and adequate renal function (creatinine serum $<$1.2 mg/dl). Excluded patients were those with a history of hypersensitivity to the test drug or preparations containing Polysorbate 80, serious concurrent disease or apparent infection with fever, pregnant or lactating women or women who may possibly be pregnant, and other patients considered by the attending physician to be unsuitable for participation in the study. Criteria for discontinuation of therapy were defined as apparent exacerbation of the disease or a serious complication, or a serious adverse event making continuation of treatment difficult, interruption of radiation for two consecutive weeks, refusal of the patient to continue therapy, or any other condition judged by the attending physician to contraindicate continued therapy. If the disease process was evaluated as no change or progressive disease (NC/PD) at the end of 3 weeks or more after the initiation of treatment, the present therapy could be discontinued and replaced by another therapy. This study was conducted in accordance with the *Guidelines for the Clinical Evaluation of Antineoplastic Drugs* based on the ethical principles of the Declaration of Helsinki, and in compliance with Standards for Good Clinical Practice (GCP), after approval by the institutional review board of Tokyo Medical University.

Treatment Schedule

The approved dose and schedule for DOC in head and neck cancer in Japan is 60–70 mg/m^2 every 3–4 weeks. In general, 60 mg/m^2 DOC is given every 4 weeks, thus the dose intensity is calculated as 60 mg/m^2/4 weeks. The bi-weekly dose intensity is calculated as 30 mg/m^2/2 weeks, which was considered enough to enhance the cytotoxic effect. In lung cancer, bi-weekly DOC plus carboplatin (CBDCA) with concurrent radiation therapy in patients with unresectable stage, non-small cell lung cancer has been reported (7). The dose of DOC was administered 30 mg/m^2 and CBDCA was area under the curve (AUC) 3 on Day 1, 15, 29, 43 and 60 Gy radiation was concurrently delivered. This report showed a high response rate (90%) and the grade 3–4 toxicities were neutropenia in 6%, esophagitis in 3% and pneumonia in 9%; thus the toxicity was tolerable. Considering this report, we set the starting dose level (level 1) of DOC at 30 mg/m^2, level 2 at 35 mg/m^2 and level 3 at 40 mg/m^2; level 0 (25 mg/m^2) was set for when severe toxicity occurred. DOC was administered on days 1, 15 and 29.

We gave radiotherapy to the primary and neck regions once a day at 4 MeV photons, using the cone-down technique, and limiting the radiation field to the primary tumor site and/or involved lymph node with a sufficient margin. The radiation fields in the phase I and the phase II studies are shown in Tables 1 and 3. We gave 30 fractions of 2 Gy at each rate totaling 60 Gy of five fractions per week. Once 40 Gy had been delivered, the spinal cord was excluded, and the clinical

Table 1. Characteristics of patients at each level

	Case	Sex	Age	Performance status	Primary site	Stage	Radiation field
Level 1	1-1	M	50	0	Larynx	T2N1M0	6 × 8
	1-2	M	62	0	Larynx	T2N0M0	6 × 6
	1-3	M	70	0	Hypopharynx	T2N1M0	17 × 13
Level 2	2-1	M	69	0	Larynx	T2N0M0	6 × 6
	2-2	M	56	0	Hypopharynx	T2N1M0	17 × 13
	2-3	M	70	0	Larynx	T2N0M0	6 × 6
	2-4	M	58	0	Larynx	T2N1M0	6 × 8
	2-5	F	70	0	Hypopharynx	T2rN0M0	13 × 10
	2-6	M	50	0	Hypopharynx	T2N1M0	16 × 12
Level 3	3-1	M	52	0	Hypopharynx	T2N1M0	17 × 13
	3-2	M	58	0	Larynx	T2N1M0	6 × 8
	3-3	M	60	0	Larynx	T2N1M0	6 × 8

target volume was reduced to only the primary region and involved neck nodes. Figure 1 shows the treatment schedule.

Dose Escalation and Definition of Dose-limiting Toxicity

The dose was at level 1 initially, and, if level 1 was not achieved, it was reduced to level 0 and the patient was followed carefully. If level 1 was achieved, the dose was increased to level 2. Three patients were assigned to each dose level, and if one or two patients showed DLT, three patients were added at the same dose level, to allow six patients to make up a cohort. If DLT was not detected in three or more of six patients, a dose higher by one level was administered to three new patients. If DLT was recognized in three of three patients or three or more of six patients, that dose level was regarded as the MTD, and the dose was not increased thereafter. The dose was also not increased in the remaining same-level patients. On the basis of the above principles, the Efficacy Safety Evaluation Committee judged whether or not to step up the dose level. DLT was defined as grade 4 leukopenia or neutropenia continuing for more than 5 days even with G-CSF, grade 4 neutropenia with fever (>38°C) even with G-CSF rescue, platelet count less than 30 000/mm^3 and grade 3 or 4 non-hematological toxicity, excluding nausea, vomiting, anorexia, fatigue and stomatitis, based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

Treatment Assessment and Statistical Methods

Tumors were assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI) scan every 2 weeks after the initial day of treatment. Patients were assessed within 4 weeks after completing three cycles of DOC plus 60 Gy of radiation. Safety was assessed every week. All patients were assessed for recurrence by endoscopy every 4 weeks, and CT scan or MRI scan every 3 months after the treatment. The design of this study was based on a binominal distribution with no planned interim analysis. In the phase II part of this study, the primary end point was the overall response rate (ORR). Assuming a null hypothesis of a 70% ORR, with a one-sided α error of 0.05 and β error of 0.2, it was necessary to enroll a minimum of 24 patients at the recommended dose (RD), including those treated at the RD during the phase I part of the study. The secondary endpoints were the protocol implementation rate, rate of preservation of the larynx and survival outcome.

RESULTS

Phase I Study

Table 1 shows the characteristics of the patients. In three patients at level 1 adverse reactions of grade 3 or more were not observed, while grade 2 mucositis was seen in two patients and radiation dermatitis in all patients. At level 2, 1 patient with hypopharyngeal cancer developed an eating disorder, which required intravenous hyperalimentation (IVH) management, so that this was evaluated as grade 4 toxicity. For this reason, three patients were added. In one additional patient with hypopharyngeal cancer, grade 4 mucositis appeared. Grade 4 toxicity occurred in two of six patients, but another four patients had only grade 2 adverse event and did not show DLT. In three patients at level 3, one patient with laryngeal cancer had only grade 2 adverse events, but one patient with hypopharyngeal cancer developed grade 4 mucositis, and another patient with laryngeal cancer developed serious blood toxicity when the second dose of DOC was given and the radiation dose reached 40 Gy, and disseminated intravascular coagulation (DIC) turned into septicemia, requiring dialysis in the ICU. This patient was saved and in the 3 years since then, the primary lesion and cervical metastasis have been controlled and the patient's activities of daily living have not been compromised. Toxicities in the above two patients were judged to be DLT, and level 3 was set as the MTD. From these findings, RD was placed at level 2, which was 35 mg/m^2. Table 2 shows the occurrence of toxicities at each level. Apart from the DIC in the patient with laryngeal cancer, grade 4 mucositis occurred in a patient with hypopharyngeal cancer with an irradiation field of 17 × 13 cm, and it seemed highly likely that the level 3 dose could be tolerated in laryngeal cancers that require only 6 × 6–8 cm narrow fields of irradiation. The present series of patients has been followed up for at least 3 years. The larynx was preserved in all patients and no recurrence was observed during follow-up.

Table 2. Occurrence of toxicity at each level

Grade	Level 1 (n = 3)					Level 2 (n = 6)					Level 3 (n = 3)				
	1	2	3	4	3/4 (%)	1	2	3	4	3/4 (%)	1	2	3	4	3/4 (%)
Leukopenia	1					1						1	1	1	67
Anemia	1					1								1	33
Thrombopenia														1	33
Nausea	1					1									
Fatigue	2					1	3				1		2		67
Loss of appetite	2					2	3		2	33			1	1	67
Mucositis	1	2				3			2	33		1	1	1	67
Liver function disorder							2					2		1	33
Radiodermatitis		3					4		2	33		1	2		33
Flash						1									
Fever															
Infection						1						1		1	33

Table 3. Characteristics and outcome of patients at Phase II study

Laryngeal cancer cases

Case	Sex	Age	PS	Stage	RT field	Outcome	Course
1	M	56	0	T2N0M0	6 × 8	CR 40 M	
2	M	64	0	T2N1M0	6 × 6	CR 40 M	
3	M	59	0	T2N0M0	6 × 6	CR 37 M	
4	M	64	0	T2N1M0	6 × 8	CR 38 M	
5	M	70	0	T3N0M0	6 × 8	CR 36 M	
6	M	74	0	T2N0M0	6 × 6	CR 39 M	
7	M	71	0	T2N1M0	6 × 8	CR 38 M	
8	M	69	0	T2N0M0	6 × 6	CR 36 M	
9	M	70	0	T2N0M0	6 × 6	CR 36 M	
10	M	58	0	T2N1M0	6 × 8	CR 36 M	

Hypopharyngeal cancer cases

Case	Sex	Age	PS	Stage	RT field	Outcome	Course
1	M	75	0	T2N1M0	17 × 13	CR 40 M	
2	F	70	0	T2N0M0	13 × 10	CR 39 M	
3	M	50	0	T2N1M0	17 × 13	CR 39 M	
4	M	48	0	T2N1M0	16 × 12	CR 36 M	
5	M	63	0	T2N1M0	17 × 13	PR 38 M	30Gy/pharygolarygectomy
6	M	63	0	T3N0M0	17 × 13	CR 37 M	
7	M	75	0	T3N0M0	17 × 13	CR 37 M	
8	M	72	0	T2N1M0	17 × 13	PR 38 M	Neck dissection
9	M	75	0	T2N0M0	15 × 13	CR 37 M	
10	M	46	0	T2N1M0	17 × 13	PR 37 M	Neck dissection
11	M	55	0	T2N0M0	17 × 13	CR 38 M	
12	F	61	0	T2N0M0	15 × 10	CR 38 M	
13	F	70	0	T2N0M0	13 × 10	CR 36 M	
14	M	50	0	T2N1M0	16 × 12	CR 36 M	
15	M	56	0	T2N1M0	17 × 13	CR 36 M	

Phase II Study

In 10 patients with laryngeal cancer and 15 patients with hypopharyngeal cancer, the DOC dosage was fixed at 35 mg/m^2 and the same protocol was used. About half of the 25 patients were treated on an outpatient basis. Table 3 shows the characteristics of patients and outcome of patients of the phase II study. In three hypopharyngeal cancer cases, the local lesion could not be controlled and pharyngolaryngectomy with resection of the cervical esophagus had to be performed in one patient, and neck dissection in two patients. The protocol implementation rate was 100% in laryngeal cancer and 93.3% in hypopharyngeal cancer because surgery was performed on one patient when 30 Gy of radiation had been delivered. Overall, treatment was completed without interruption in 24 patients, with a protocol implementation rate of 96%, which proved that this protocol was tolerable. In laryngeal cancer, all patients (100%) achieved complete response (CR). Adequate effect can these be anticipated even in patients with T2-3N1 cancer. In hypopharyngeal cancer, the primary lesion was surgically treated in one patient, and neck dissection alone was additionally performed in two patients. Twelve patients achieved CR, and the CR rate was 80%. Three patients

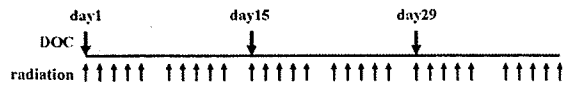

Figure 1. treatment schedule for docetaxel (DOC) administration and radiation.

Table 4. Occurrence of toxicity at phase II study

Grade	Larynx ($n = 10$)					Hypopharynx ($n = 15$)					Total ($n = 25$)				
	1	2	3	4	(3/4) (%)	1	2	3	4	(3/4) (%)	1	2	3	4	(3/4) (%)
Leukopenia	1	1				1	1	2			2	2	2		8
Anemia	1					1	2	2		13	2	2	2		8
Thrombopenia	1										1				
Nausea	1					3					4				
Fatigue	2	2				1	3	2		13	3	5	2		8
Loss of appetite	1	2	2		20	2	2		2	13	3	4	2	2	16
Mucositis	1	4	2		20		5	4	3	47	1	9	6	3	36
Liver function disorder							2					2			
Radiodermatitis		3	2		20		10	3		20		13	5		20
Flash	1					1					2				
Fever						1					1				
Infection						1					1				

achieved partial response (PR). Since CR was obtained even in patients with T3 cancer and the larynx was lost only in one of 10 patients, the present treatment was considered sufficiently effective. The ORR was 100%. The overall local control rate was 92% because surgery was performed, but operation consisted only of neck dissection in two patients. The rate of laryngeal preservation was 100% in the laryngeal cancer group and 93.3% in the hypopharyngeal cancer group, 96% in total. All patients treated by the present method have been alive for at least 3 years without recurrence. Table 4 shows the occurrence of toxicity in the phase II study. Grade 3 or 4 adverse events consisted of mucositis in 36%, radiodermatitis in 20%, and loss of appetite in 16% of the patients. Their toxicities were manageable. It has been demonstrated that bi-weekly docetaxel combined with radiation therapy for cancer of the larynx/hypopharynx is an extremely effective treatment, provided that it is indicated for the specific stage of cancer.

DISCUSSION

The incidence of head and neck cancer is gradually increasing with the increased aging of the society, and a 1995 report estimated the annual incidence to be approximately 40 000 in the Unites States (8). However, prognosis has not dramatically improved in advanced squamous cell carcinoma of the head and neck, and the prospect of functional preservation is still poor, even with multidisciplinary treatment. Since squamous cell carcinoma, which accounts for the majority of head and neck cancers, is sensitive to radiation to a certain degree, there is hope for a new therapy involving powerful chemotherapy incorporated with curative treatment regimens. Various chemoradiation therapies have been tried using 5-FU, bleomycin, mitomycin, methotrexate among others. Since 1977, when the usefulness of cisplatin for head and neck cancers was reported (9), the efficacy of combination chemotherapy with multiple drugs including cisplatin has been reported, and multi-agent chemotherapy using cisplatin as the chief drug is utilized at present (10,11).

Meanwhile, the reviews of chemoradiation therapy for advanced head and neck cancers have showed that, in many clinical trials comparing chemoradiation therapy using cisplatin (or carboplatin) $\pm$ 5-FU with radiation therapy alone, the combination therapy group compared favorably with the radiation-only group with respect to local control rate and survival rate (12,13). With the progress of reconstructive surgery, survival rates are improving thanks to extended surgery. However, larygectomy or pharygolarygectomy means loss of phonation and swallowing functions, and a great deterioration in quality of life. Recently, chemoradiation therapy has been used to preserve the organ in consideration of the quality of life while achieving permanent cure by radiation therapy as far as possible, and large-scale clinical studies are being conducted such as the Veterans Administration Lung Cancer Study Group and Groupe d'Etude des Tumeurs de la Tete et du Cou for improvement of the prognosis of advanced cancer or preservation of organs (14–16).

More recently, studies have been conducted on combination of radiation with taxanes, which synchronize cells in the M phase, which is most sensitive to radiation (17,18). In Japan, a late phase II clinical study of DOC in advanced/recurrent head and neck cancers was conducted in 29 institutions between April 1995 and August 1997. In 63 patients eligible for evaluation (therapy completed in 59 patients),

the response of tumor was CR in one patient and PR in 13 patients, thus the response rate was 22.2%. Major adverse effects with grade 3 or higher were leukopenia in 59.7% and neutropenia in 79.0% (19). In addition, a phase I/II study of weekly DOC and radiation for head and neck cancer in Japanese was conducted; the RD of weekly DOC was decided at 10 mg/m^2 and the ORR was 96.9%. However, the CR rate of primary site was 59.4% (5). We considered the dosage insufficient for enhancing cytotoxic effect, and sufficient only for radiosensitization effect.

To improve the rate of laryngeal preservation, we evaluated, using the occurrence of adverse events as an index, the tolerability of a combination therapy with bi-weekly DOC administration and radiation, which can be expected to produce a cytotoxic effect, and determined MTD as well as the RD for T2N0-1M0, T3N0M0 hypopharyngeal cancer or T2N0-1M0, T3N0-1M0 laryngeal cancer. T3N1M0 hypopharyngeal cancer was omitted, since such cases undergo surgery. In the phase I study, the DLT was mucositis and neutropenia at level 3, and the MTD was 40 mg/m^2. Particularly in hypopharyngeal cancer, grade 3 or higher mucositis and swallowing disorder occurred because of the greater size of the irradiation field, but the recommended dose was placed at 35 mg/m^2. The phase II study was conducted with a DOC dosage of 35 mg/m^2 using the same schedule. In the phase II study, 10 patients with laryngeal cancer and 15 patients with hypopharygeal cancer were enrolled. The protocol implementation rate was 96%, the CR rate was 100% in laryngeal cancer and 80% in hypopharyngeal cancer, and total (including PR) ORR was 100%. The larynx preservation rate was 96%, and the overall local control rate was 92%. From these results, the present treatment appears to be indicated in patients with advanced N stage if combined with planned neck dissection, etc. All patients have been alive for at least 3 years without any recurrence. Since this protocol was applicable on an outpatient basis, this seemed to have greater benefit to patients than cisplatin-based chemoradiotherapy. This protocol is extremely useful provided that it is indicated for the specific stage of cancer.

Conflict of interest statement
None declared.

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Acta Oto-Laryngologica, 2008; 128: 578–582

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ORIGINAL ARTICLE

Useful combination of intra-arterial chemotherapy and radiation therapy for lateral oropharyngeal wall cancer

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Abstract

Conclusion: A concomitant treatment of intra-arterial chemotherapy and radiation therapy is a promising therapeutic option for oropharyngeal cancers. *Objectives:* Treatment for oropharyngeal cancer has been far from standardized because of its pathophysiologic complexity and its low incidence. In our department, T1 stage tumors with N0 or N1 status are primarily treated surgically, while T1 tumors with N2 or more advanced lymph node involvement are additionally treated with concomitant chemoradiotherapy (CRT). Treatment for T2, T3, and T4 tumors is based on CRT, but surgery is also performed if necessary. *Patients and methods:* The study included 73 patients with squamous cell carcinomas of the lateral oropharyngeal wall who received first-line therapy at our department between May 1993 and October 2003. *Results:* The 5-year disease-specific survival by disease stage was 100% for stage I, 90.9% for stage II, 88.2% for stage III, 69.8% for stage Iva, and 22.2% for stage IVb. The overall 5-year disease-specific survival was 71.8%, and the overall 5-year crude survival was 54.1%.

Keywords: *Oropharyngeal wall cancer, T classification, N classification, stage classification, radiotherapy, combination therapy*

Introduction

The oropharynx is directly involved in deglutition and articulation. Treatment for oropharyngeal cancer has been far from standardized because of its pathophysiologic complexity and its low incidence. Currently, radiotherapy (RT) and/or surgery are the common options for treatment of oropharyngeal cancers. It has been reported that concomitant chemoradiotherapy (CRT) is more successful in local control of head and neck cancers than RT [1,2].

Tumor recurrence developing at the parapharyngeal lymph nodes makes salvage therapy difficult and the parapharyngeal lymph nodes can be included in the same radiation field as the primary lesion. It is recommended that surrounding lymphatic tissues are treated simultaneously with the primary tumor. In our local therapy, both the primary lesion and the parapharyngeal space are targeted and CRT is the primary choice for the therapy of these targets. A combination of intra-arterial chemotherapy and RT is effective for achieving local control of oropharyngeal cancer [3]. We administer an anticancer agent by retrograde injection into the superficial cervical artery to achieve a high level of anticancer agent at the lesion. To evaluate the arterial drug delivery system in our therapeutic policy, we studied the outcome compared with other reports on therapy for lateral oropharyngeal wall cancer.

Patients and methods

Therapeutic strategy for treatment of oropharyngeal malignancies

Our approach to locoregional treatment for oropharyngeal cancer is shown in Figure 1. To effectively achieve localized control of both the primary lesion and the parapharyngeal lymph

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(Received 9 August 2006; accepted 5 October 2006)

ISSN 0001-6489 print/ISSN 1651-2551 online
DOI: 10.1080/00016480601053073

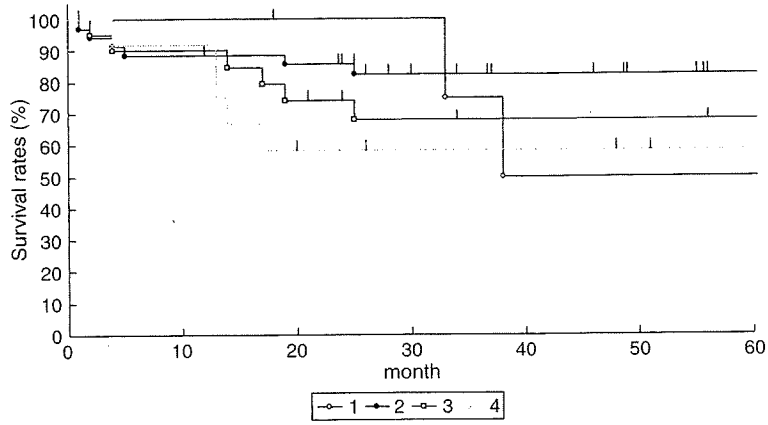

Figure 1. Disease-specific survival rates by T classification.

node, T1 stage tumors with N0 or N1 status are primarily treated surgically, while T1 tumors with N2 or more advanced lymph node involvement are additionally treated with CRT. Treatment for T2, T3, and T4 tumors is based on CRT, but surgery is also performed if necessary. In CRT, *cis*-diammined dichloroplatinum (CDDP) and 4'-*O*-tetrahydropyranyl adriamycin (THP) are mainly administered with other anticancer agents by the usual route via retrograde injection into the superficial temporal artery. Indigo carmine dye was used to determine the position of the tip of the catheter, which was detained around the ascending pharyngeal artery and facial artery. CDDP (5 mg/m^2/day) was infused through a catheter 1 h before RT on days 1–5, 8–12, 15–19, and 22–26 in accordance with the RT schedule. In case of either 40–60 ml/min obtained by creatinine clearance test or age >70 years, all dosages were cut off to 70%. THP (10 mg/day on days 1–5 and 8–11 between 1993 and 1997, and on days 1–5 and 8–12 between 1998 and 2003) was infused through a catheter 1 h before RT in accordance with the RT schedule. Preoperatively total radiation doses of CRT and RT alone were 40 Gy and 60–70 Gy, respectively.

When there is no lymph nodes metastasis (N0), cervical lymph node resection is not essential; however, when the primary tumor is surgically removed through a cervical approach, cervical lymph nodes are also resected. When there is involvement of lymph nodes (N1 or higher), cervical lymph node resection is performed.

Patients

The study included 73 patients with squamous cell carcinomas of the lateral oropharyngeal wall who received first-line therapy at our department between May 1993 and October 2003. The mean age was 63.1 (range 44–85 years), and follow-up periods ranged from 21 months and completed at 60 months.

The following were examined: 1) TN staging; 2) the method for localized therapy; 3) T staging of localized recurrent tumors and therapeutic method; 4) the control rate of primary tumor; 5) 5-year disease-specific survival in which only deaths from the primary disease were counted and 5-year cumulative crude survival which included all deaths. The Kaplan-Meier method was used for statistical analysis of survival data. The log rank test was used to examine the significance of differences, and a p value of <0.05 was considered statistically significant.

Results

TN classification

The TN classification of oropharyngeal tumors in our study is shown in Table I. T1 tumors were observed in 5 cases (6.8%), T2 in 35 (47.9%), T3 in 21 (28.8%), and T4 in 12 (16.4%). There were 21 cases (28.8%) of N0, 12 cases of N1 (16.4%), 31 cases of N2 (42.5%), and 9 cases of N3 (12.3%). Stage III and IV tumors accounted for 60 cases (82.2%) among all patients.

Methods for localized therapy

CRT was performed in 48 cases (65.8%), surgery in 12 (16.4%), RT in 12 (16.4%), and chemotherapy

Table I. TN classification.

	N0	N1	N2a	N2b	N2C	N3	Total
T1	2	0	0	2	0	1	5
T2	10	8	3	6	3	5	35
T3	8	2	3	4	3	1	21
T4	1	2	3	1	3	2	12
Total	21	12	9	13	9	9	73

(CT) in 1 (1.4%) for locoregional control. Of 48 patietns who received CRT, 8 underwent planned surgery for removal of the primary lesion or cervical lymph node metastasis, and 1 received surgical salvage. Of 12 patients who were treated with RT, staged surgery was performed in 2 patients.

Localized therapy of T staging is summarized in Table II. T1: three CRT cases and two surgical cases. T2: 27 CRT cases, 2 surgical cases, 5 RT cases, and 1 CT case. Of the 27 CRT cases classified as T2, 1 received staged surgery, and in another case surgical salvage therapy was performed. T3: 12 CRT cases, 5 surgical cases and 4 RT cases. Of the 12 CRT cases, three were treated with 40 Gy before surgery. T4: six CRT cases, three surgical cases, and three RT cases. Staged surgery was performed in three of these six CRT cases and in two of the three RT cases.

Therapeutic methods for localized recurrent tumors by T classification

T2 recurrent tumors developed in two cases (one RT and one surgical case), T3 in four cases (one CRT case who later received a surgical treatment and three RT cases), and T4 in three cases (two CRT and one surgical case).

Local control rates

The local control rates for primary tumors were 100% (4/4) for T1, 94.3% (33/35) for T2, 85.7% (17/21) for T3, and 66.7% (9/12) for T4. The overall local control rate was 87.7% (64/73).

5-year survival

The 5-year disease-specific survival rates by T classification are shown in Figure 1. The 5-year disease-specific survival was 50% for T1, 82.4% for T2, 67.9% for T3, and 58.3% for T4, indicating no significant difference by T staging. The 5-year crude survival was 50% for T1, 59.4% for T2, 50% for T3, and 48.6% for T4.

Figure 2 shows the disease-specific survival by N classification. The 5-year disease-specific survival was 90.2% for N0, 91.7% for N1, 66.2% for N2, and 22.2% for N3. There was a significant difference between N0 and N3 tumors ($p < 0.005$), between N1 and N3 ($p < 0.005$), and between N2 and N3 ($p < 0.01$). The 5-year crude survival was 63.6% in N0 cases, 83.3% in N1 cases, 43.9% in N2 cases, and 22.2% in N3 cases.

Table II. Methods for localized therapy.

	CRT	S	RT	CT
T1	3	2	0	0
T2	27	2	5	1
T3	12	5	4	0
T4	6	3	3	0

As shown in Figure 3, the 5-year disease-specific survival by disease stage was 100% for stage I, 90.9% for stage II, 88.2% for stage III, 69.8% for stage IVa, and 22.2% for stage IVb. There was a significant difference between stages II and IVb ($p < 0.05$), between stages III and IVb ($p < 0.001$), and between stages IVa and IVb ($p < 0.005$). The 5-year crude survival was 100% for stage I, 53.0% for stage II, 75.6% for stage III, 49.2% for stage Iva, and 22.2% for stage IVb. The overall 5-year disease-specific survival was 71.8% and the overall 5-year crude survival was 54.1%. There were only four stage I cases and statistical significance was not found by comparison with any other stage group.

Discussion

In our hospital, CRT is the primary choice of therapy, since we emphasize organ preservation and locoregional control. In this study, CRT was performed in 65.8% of cases. Other cases received RT alone due to systemic complications or underwent surgery only, since they had radiation intolerance. One treatment-related death occurred in a patient who was treated with CT alone. It has been reported that when treated with RT alone, the local control rates of lateral oropharyngeal wall cancer were 77% for T1 and T2, and 68% for T3 and T4 [4]. Compared with these results, our approach was favorable, with local control rates of 100% for T1, 94.3% for T2, 85.7% for T3, and 66.7% for T4. In patients who underwent CRT, the control rates of primary tumors were 100% for T1, 100% for T2, 91.7% for T3, and 66.7% for T4. It is effective for local control to achieve a high level of anticancer agent at the primary lesion and the parapharyngeal lymph node. Although CRT improves local organ preservation, further studies are necessary not only for control of early-stage symptoms such as hyposalivation, dysphagia, dysgeusia, and pigmentation but also for long-term management of late-onset dysfunctions.

The 5-year disease-specific survival rates by T staging were 50% for T1, 82.4% for T2, 67.9% for T3, and 58.3% for T4. Although the survival rate decreased with the stages, it did not show statistically significant difference among stages. The survival rate for T1 tumors was 50% because these T1 cases included three advanced-stage cancers with two cases of N2b and one of N3. Furthermore, two of these three cases had lung metastases. In oropharyngeal cancer the T and N classifications often do

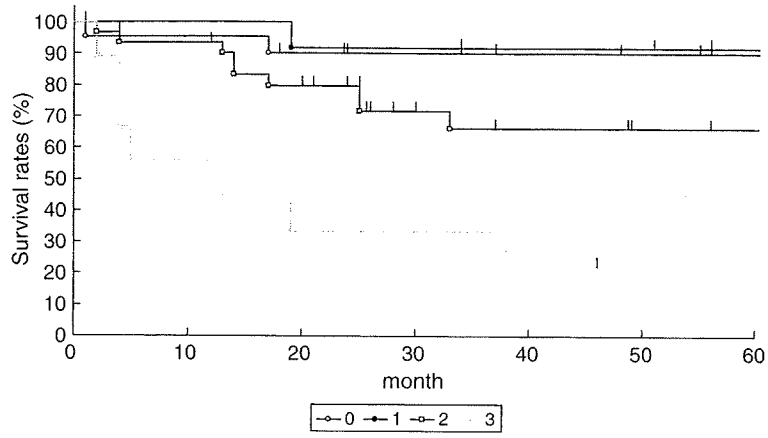

Figure 2. Disease-specific survival rates by N classification.

not correlate with each other. Also in our study, 70% of T1 and T2 cases had cervical lymph node metastases, supporting the concept that there is no association between the T and N classifications in this type of cancer.

The survival rates were 90.2% for N0, 91.7% for N1, 66.2% for N2, and 22.2% for N3, progressively decreasing with N classification. Prognosis of N3 cases was especially poor, with significant differences from the survival rates of N0, N1, and N2 tumors. The survival also decreased with disease stages: 100% for stage I; 90.9% for stage II; 88.2% for stage III; 69.8% for stage IVa, and 22.2% for stage IVb. Stage IVb tumors showed statistically significantly poorer prognosis. Since stage IVb includes any T/N3 tumors, this result also reflected the poor prognosis of N3 tumors. Our approach resulted in a 5-year disease-specific survival of 71.8%, which was satisfactory compared with 54–71% 5-year disease-specific survival at other facilities [5–8]. Our study suggested that an improvement of local control by CRT advances the 5-year disease-specific survival. However, the 5-year crude survival was only 54.1%, even though the local control rate and 5-year disease-specific survival were favorable. Other studies have shown similar results (crude survival, 38–60% [5–8]). Since oropharyngeal cancer is often associated with the development of multiple cancers [9], it is desirable to construct a therapeutic strategy with a view to addressing this situation, especially in young patients. Even when oropharyngeal cancer is treated with CRT, it is still difficult to treat multiple cancers, and therein lies a future challenge.

In conclusion, our results suggest that a concomitant treatment of intra-arterial chemotherapy and RT raises the local control rates and that the therapeutic index is improved by this concomitant treatment of oropharyngeal cancers.

Acknowledgement

The authors are indebted to Prof. J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review and Prof. Yasuo Watanabe (Department of Pharmacology and Pharmacotherapy, Nihon Pharmaceutical University) for his critical comments on this manuscript.

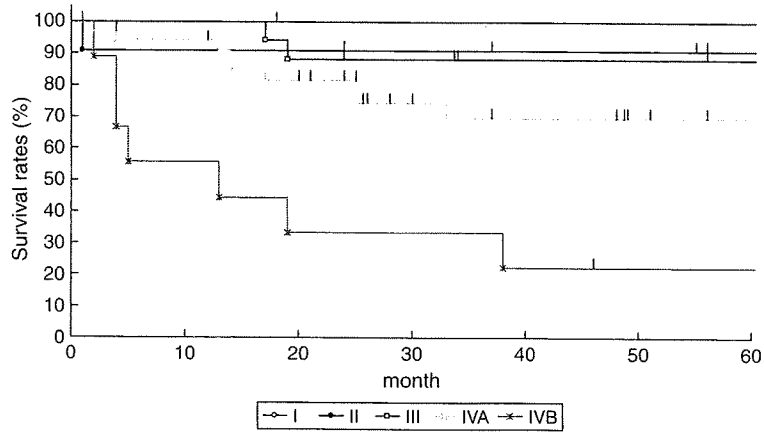

Figure 3. Disease-specific survival rates by stage classification.

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