分担研究報告書

厚生労働科学研究費補助金（がん臨床研究事業）

頭頸部腫瘍に対するIMRTの有用性に関する研究

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研究要旨

1998年のAl-Sarrafの報告(JCO)以降当院では上咽頭癌の治療は化学放射線同時併用療法を原則としている。併用化学療法として2000年-2005年まではCDDP/5-FU(FP)を照射中に2コース、それ以降は2011年まではweekly CDDP(wCDDP)を照射中に5コースを原則として治療を行った。また照射法として2000-2004年までは3DCRT, 2005年以降は原則強度変調放射線治療（IMRT）で治療を行った。併用化学療法の違いにおける治療成績、およびIMRT導入による照射後口腔内乾燥症の程度について検討を行ったところ3年全生存率、局所制御率及び無増悪生存期間はそれぞれFP群で84,82,58%、wCDDP群で90,72,49%でありいずれも2群間に有意差は認めなかった。急性期有害事象はFP群に比しwCDDP群の方が皮膚炎は軽度、白血球減少の頻度が高い傾向にあった。照射後口腔内乾燥に関してはIMRT治療例の方が3DCRTに比し軽度である傾向が認められた。

A. 研究目的

1998年のAl-Sarrafの報告(JCO)以降当院では上咽頭癌の治療は化学放射線同時併用療法を原則としている。併用化学療法として2000年-2005年まではCDDP/5-FU(FP)を照射中に2コース、それ以降は2011年まではweekly CDDP(wCDDP)を照射中に5コースを原則として治療を行った。また照射法としては2000-2004年までは3DCRT, 2005年以降は原則強度変調放射線治療（IMRT）で治療を行った。併用化学療法の違いにおける治療成績、およびIMRT導入による照射後口腔内乾燥症の変化について検討を行った。

B. 研究方法

2000年から2010年の期間中、当院で化学放射線同時併用療法を施行したII-IV期上咽頭癌患者に関し治療成績、有害事象を調べ併用化学療法別に後ろ向きに比較検討を行うとともにIMRTの導入前後における放射線治療後の口腔内乾燥の程度を比較検討した。

（倫理面への配慮）

国の倫理指針および当院自主臨床研究事務局によって承認された内容を遵守し研究を行った。患者のプライバシーの保護に十分配慮し、個人情報が流出しないように細心の注意を払った。

C. 研究結果

FP群、wCDDP群共に25例であった。観察期

間は FP 群 7-118 ヶ月（中央値 71)、wCDDP 群 8-62 ヶ月（中央値 34)。wCDDP 群の方が stage Ⅱの症例数が多くⅢが少なかった。3 年全生存率、局所制御率及び無増悪生存期間はそれぞれ FP 群で 84,82,58%、wCDDP 群で 90,72,49%でありいずれも 2 群間に有意差は認めなかった。急性期有害事象は FP 群に比し wCDDP 群の方が皮膚炎は軽度、白血球減少の頻度が高い傾向にあった。照射後口腔内乾燥に関しては IMRT 治療例の方が 3DCRT に比し軽度である傾向が認められた。

D. 考察

無増悪生存期間に関し有意差はないが wCDDP 群の方が低いのは実際の CDDP 投与回数が平均で 4 回であり FP 比較し化学療法の強度が弱かった可能性がある。FP 群の方が皮膚炎が強いのは 5-FU が含まれているためと考えられた。

E. 結論

今回の検討では急性期有害事象の違いはあるが 2 つの併用化学療法間で治療成績に差は認められなかった。IMRT により口腔内乾燥は軽度となる傾向があった。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

Kazuhiko Tsuchiya, Koichi Yasuda, Yukiko Nishikawa, Rumiko Kinoshita, Rikiya Onimaru, Hiroki Shirato: Retrospective comparison between Cisplatin plus fluorouracil and weekly Cisplatin in concurrent chemotherapy setting for stage II-IV nasopharyngeal carcinoma: Hokkaido University Hospital experience. ASTRO 54th Annual meeting, Boston, 2012.10.28-31

H. 知的財産権の出願・登録状況

特になし

分担研究報告書

厚生労働科学研究費補助金（がん臨床研究事業）

頭頸部腫瘍に対するIMRTの有用性に関する研究

分担研究者　村上　祐司　　（広島大学病院　放射線治療科　）

研究要旨

本研究では、当院の咽頭癌に対する強度変調放射線治療（IMRT/VMAT）の初期治療結果を解析し、本治療の有用性を検討する。対象は、09年10月から12年6月に本法を施行した上/中/下咽頭癌12/15/9例である。線量処方はD95=96-100%で、SIB法(33例)では肉眼病変/高リスク予防域/予防域に70/63/56 Gyを35分割で投与、2-step法(3例)では予防域に46 Gy/23分割照射後、肉眼病変に24 Gy/12分割を追加照射した。全例に化学療法を同時併用した。観察期間中央値15ヶ月で、2年全生存/局所領域制御率は、上咽頭90%/92%、中下咽頭93%/81%、全例92%/84%、再発の主体は遠隔転移であった。≥G2口内乾燥は照射直後83%に認めたが、治療後6ヶ月時30%に減少した。本法による局所制御率は良好で従来法と遜色なかった。再発は遠隔転移が主体で、多剤併用化学療法や分子標的薬を含めた新たな全身療法についての検討が必要である。唾液腺障害は経時的に改善を認め、本治療の有用性が示唆された。しかし、疾患毎の至適な標的設定、リスク臓器の線量制約設定など、標準的治療方法確立のためにはさらなる検討が必要である。また、多大な労力と時間を要する治療計画の補助ツールが開発されており、これら補助ツールの臨床的有用性を検討中である。これらを通じて、IMRTの件数増加、本邦での施行施設増加につながれば、より多くの患者に貢献できる。

A　.研究目的

当院では、2008年7月より前立腺癌治療に強度変調放射線治療(Intensity modulated radiotherapy: IMRT)を導入、2009年10月からは頭頚部癌に対するIMRTを開始した。固定多門IMRTにて開始したが、高精度放射線治療患者数増加、治療スループット向上、MU値低減目的にVMATを導入した。今回は、当院にて施行した上咽頭癌、中下咽頭癌に対するIMRT/VMATの初期治療結果を解析し、本治療の頭頚部癌に対する有用性を検討する。

B.　研究方法

対象は、2009年10月から2012年6月にかけて、当院にてIMRT/VMATを施行した上咽頭癌/中下咽頭癌36例。年齢中央値64歳(34-85歳)、男性/女性28/8例、原発部位は上/中/下咽頭12/15/9例であった。上咽頭癌の組織型は、Sqcc/Lymphoepithelial ca/Undifferenciated ca/他が6/1/2/3例、病期はI/II/III/IVが0/5/4/3例であった。中下咽頭癌はSqcc/Lymphoepithelial caが21/3例、I/II/III/IVが0/2/2/20例であった。放射線治療は、固定多門IMRT/VMATを6/30

例に施行し、SIB 法を 33 例、2-step 法を 3 例に施行した。線量処方は D95=96-100%（中央値 100%）で、SIB 法では、肉眼病変/高リスク予防域/予防域に 70/63/56 Gy を 35 分割で投与、2-step 法では、予防域に 46Gy/23 分割照射後、肉眼病変に 24Gy/12 分割を追加照射した。耳下腺、脊髄、脳幹などリスク臓器は可能な限り線量低減を試みた。全例に化学療法を同時併用し、CDDP+5FU 22 例、CDDP 単剤 10 例、他 4 例であった。

なお、本研究は回顧的な解析であり、患者の個人情報が院外に持ち出されることはない。

C .研究結果

上咽頭癌 1 例(8%)と中下咽頭癌 7 例(29%)に頚部郭清が施行された。観察期間中央値 15 ヶ月。再燃再発は 9 例(25%)に認め、遠隔 6 例(17%)、局所領域 3 例(8%)であった。2 年全生存/無再発生存/局所領域制御率は、上咽頭 90%/48%/92%、中下咽頭 93%/77%/81%、全例 92%/64%/84%であった。≥G3 急性期有害事象は、粘膜炎 26 例(72%)、嚥下障害 26 例(72%)、皮膚炎 17 例(47%)、口内乾燥 2 例(6%)に認めた。初期 18 例と後期 18 例の比較では後期症例において≥G3 皮膚炎の発生は有意に減少した(72% vs. 22%, <0.01)。≥G2 口内乾燥は、照射直後は 83%に認めたが、治療後 6 ヶ月時 30%に減少した。他の≥G3 の晩期有害事象として喉頭浮腫(G4)を 2 例に認めた。

D .考察

本邦では2000年頃からIMRTが臨床導入され、先進医療を経て2007年に保険収載されたが、線量評価法、線量分割法、治療計画法などの施設間差は大きく、標準的治療法も確立していない。日本放射線腫瘍学会による定期構造調査（2009年）によれば、IMRT機能の付いた直線加速器は約230施設に設置されているが、マンパワーの問題などで、頭頸部腫瘍に対してIMRTを行っている施設はごくわずかであった。当院では2009年10月より頭頚部腫瘍に対するIMRTを開始した。今回の初期治療成績の解析では、IMRT/VMATによる局所制御率は良好で、従来法と遜色なかった。再発様式は遠隔転移が主体で、多剤併用化学療法や最近保険収載されたCetuximabなどの分子標的薬を含めた全身療法の至適な使用法、タイミングなどについて検討が必要である。従来法で回避困難であった唾液腺障害は、治療直後には高率に認めたが、経時的に改善を認め、IMRT/VMATの有用性が示唆された。IMRT/VMAT導入当初は、強い皮膚障害が問題となったが、皮膚への線量制約の見直し、治療計画技術の向上により、障害発現を著明に減じることができた。治療計画の自由度が高まった反面、標的の輪郭描出範囲やリスク臓器の線量調節など計画者に委ねられる因子も多く、標準的治療方法確立のためには、疾患毎の至適な標的設定、リスク臓器の線量制約設定など、さらなる検討が必要である。また、多大な労力と時間を要する治療計画の補助ツールとして、新たな自動輪郭抽出ソフトやDeformable image registrationソフトが開発されている。当院では現在、これら補助ツー

ルの臨床的有用性の検討を施行中である。これらを通じて、IMRTの件数増加、本邦での施行施設増加につながれば、より多くの患者に貢献できる。

E .結論

上中下咽頭癌に対する IMRT/VMAT では良好な局所領域制御が得られ、従来法で問題であった唾液分泌障害は減少した。さらなる治療成績、安全性向上のため、治療計画補助ツールの開発および至適補助化学療法を含めた検討を行う予定である。

F .健康危険情報：なし

G.研究発表

1.論文発表

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F. 知的財産権の出願・登録状況（予定を含む）

1．特許取得：なし

2．実用新案登録：なし

3．その他

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Head and neck cancer

Volume and dosimetric changes and initial clinical experience of a two-step adaptive intensity modulated radiation therapy (IMRT) scheme for head and neck cancer

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ABSTRACT

Purpose: The aim of this study was to show the benefit of a two-step intensity modulated radiotherapy (IMRT) method by examining geometric and dosimetric changes.
Material and Methods: Twenty patients with pharyngeal cancers treated with two-step IMRT combined with chemotherapy were included. Treatment-planning CT was done twice before IMRT (CT-1) and at the third or fourth week of IMRT for boost IMRT (CT-2). Transferred plans recalculated initial plan on CT-2 were compared with the initial plans on CT-1. Dose parameters were calculated for a total dose of 70 Gy for each plan.
Results: The volumes of primary tumors and parotid glands on CT-2 regressed significantly. Parotid glands shifted medially an average of 4.2 mm on CT-2. The mean doses of the parotid glands in the initial and transferred plans were 25.2 Gy and 30.5 Gy, respectively. D_2 (dose to 2% of the volume) doses of the spinal cord were 37.1 Gy and 39.2 Gy per 70 Gy, respectively. Of 15 patients in whom xerostomia scores could be evaluated 1–2 years after IMRT, no patient complained of grade 2 or more xerostomia.
Conclusions: This two-step IMRT method as an adaptive RT scheme could adapt to changes in body contour, target volumes and risk organs during IMRT.
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A significant advance in radiation therapy (RT) is the successful clinical use of intensity modulated radiation therapy (IMRT). IMRT is effective, especially for head and neck cancers, since the clinical target volumes (CTV) are in contiguity with organs at risk such as the salivary glands, brain stem, and spinal cord. Two randomized clinical trials comparing IMRT and conventional RT for patients with early-stage nasopharyngeal cancer (NPC) showed a significant benefit of IMRT on salivary function and quality of life (QOL) of patients [1,2].

Although it is very encouraging to use this new technique to improve the therapeutic ratio, questions remain as to whether the conformation of target coverage and normal tissue sparing may cause marginal failure [3]. As treatment planning and quality assurance (QA) of IMRT plans require a long time to prepare, most investigators use the initial IMRT plan for the whole course of IMRT. However, significant anatomic changes, including shrinking of the primary tumor or nodal masses and body weight loss during fractionated RT, have been reported for head and neck cancers [4,5]. Our previous analysis revealed that the volume of the parotid glands decreased to 74% of the initial volume during the course of IMRT [6]. These changes in body contour, target volumes and risk organs during IMRT can affect the dose distribution to the target volume and risk organs, which can be a cause of marginal recurrence or late toxicities. In fact, marginal recurrences after IMRT for head and neck cancer have been reported by several investigators [7,8].

To avoid the risk of changes in the dose distribution during IMRT of 7–8 weeks, we adopted a two-step IMRT method for head and neck cancers. For all patients, treatment-planning computed tomography (CT) was done before IMRT (CT-1) and at the third or fourth week of IMRT for the treatment planning of boost IMRT after 46–50 Gy (CT-2) [6,7]. The aim of this study was to show the benefit of our adaptive RT scheme using a two-step IMRT method by examining the geometric and dosimetric changes in patients with head and neck cancer.

Materials and methods

Patients' characteristics and treatment methods

Between February 2006 and April 2010, 20 consecutive patients with pharyngeal cancers treated by a two-step IMRT method combined with concurrent chemotherapy were analyzed. Patients and

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Table 1
Study cohort and treatment characteristics, and their clinical results.

Case	Primary site	T stage	N stage	UICC stage	Total(Boost) RT dose	Concurrent chemotherapy	Neck dissection	Parotid D_{mean}(sum)	Xerostomia at 1–2 year	Overall survival	Local control
1	HPC	T1	N2b	VI A	70(20)Gy	Cisplatin	Y	25.6	–	15 m DOD	15 m LC
2	HPC	T2	N2b	VI A	70(20)Gy	Cisplatin	Y	21.6	Grade 0	22 m DOD	9 m rec
3	HPC	T1	N2a	VI A	70(20)Gy	S-1	N	22.5	–	9 m DID	9 m LC
4	HPC	T2	N3	VI B	70(20)Gy	Cisplatin	Y	21.6	Grade 0	56 m NED	56 m LC
5	OPC	T3	N2b	VI A	70(20)Gy	Cisplatin	N	26.8	Grade 1	53 m DOD	46 m rec
6	OPC	T2	N2	VI A	60(20)Gy	Cisplatin, 5FU	Y	29.0	–	17 m DOD	6 m rec
7	OPC	T1	N2b	VI A	66(16)Gy	Cisplatin	Y	25.1	Grade 0	53 m NED	53 m LC
8	OPC	T4a	N0	VI A	70(20)Gy	Cisplatin	N	17.5	Grade 1	36 m NED	36 m LC
9	OPC	T2	N2C	VI A	66(16)Gy	CBDCA	N	24.5	–	9 m DOD	6 m rec
10	OPC	T4a	N0	VI A	70(20)Gy	Cisplatin	N	21.7	–	8 m DOD	6 m rec
11	NPC	T3	N0	III	70(20)Gy	Cisplatin	N	23.0	Grade 0	78 m NED	78 m LC
12	NPC	T2b	N1	II	70(20)Gy	Cisplatin	N	24.9	Grade 0	74 m NED	74 m LC
13	NPC	T2b	N1	II	70(20)Gy	Cisplatin	N	27.8	Grade 0	73 m NED	73 m LC
14	NPC	T3	N0	III	70(20)Gy	Cisplatin	N	23.9	Grade 0	73 m NED	73 m LC
15	NPC	T1	N0	I	70(20)Gy	Cisplatin	N	22.4	Grade 0	70 m NED	70 m LC
16	NPC	T1	N1	II	70(20)Gy	Cisplatin	N	24.8	Grade 0	68 m NED	68 m LC
17	NPC	T3	N1	III	70(20)Gy	Cisplatin	N	23.9	Grade 0	68 m NED	68 m LC
18	NPC	T3	N2	III	70(20)Gy	Cisplatin	N	23.6	Grade 0	65 m NED	65 m LC
19	NPC	T1	N2	III	70(20)Gy	Cisplatin	Y	21.4	Grade 1	59 m NED	59 m LC
20	NPC	T3	N2	III	68(20)Gy	Cisplatin	N	26.2	Grade 0	57 m NED	57 m LC

Abbreviations: HPC, hypopharyngeal cancer; OPC, oropharyngeal cancer; NPC, nasopharyngeal cancer; CBDCA, carboplatin; y, yes; n, no; m, months; NED, no evidence of the disease; DOD, died of the disease; DID, died of the intercurrent disease; LC, loco-regional control.

tumor characteristics and their clinical results are shown in Table 1. All patients were treated with whole neck IMRT to 46–50 Gy/23–25 fractions, followed by boost IMRT limited to high-risk CTV to a total dose of 60–70 Gy/30–35 fractions (median 70 Gy). The details of target definition and margins for planning target volume (PTV) has been mentioned elsewhere [7].

Of the 20 patients, 10 had NPC, six oropharyngeal cancer (OPC), and four hypopharyngeal cancer (HPC) (Table 1). Six patients were treated with neck lymph node dissection before IMRT. Most patients were treated with concurrent chemotherapy of cisplatin 80 mg/m^2 as a Japanese standard dose for 2 or 3 times.

All patients were immobilized with a thermoplastic mask covering the head, neck and shoulders (Type-S thermoplastic based system, MED-TEC, Orange City, IA). Computed tomography (CT) scans or positron emission tomography/CT (PET/CT) for treatment planning were obtained with contrast medium at 2 mm slice intervals from the head through the aortic arch. For all patients, treatment-planning CT or PET–CT was done twice before IMRT (CT-1) and at the third or fourth week of IMRT for the treatment planning of boost IMRT (CT-2) with a new thermoplastic mask. A new mask was made carefully to be the same bony alignment of the initial mask. Boost IMRT was started without split at the fifth week of IMRT. An integrated PET/CT simulation was performed at CT-1 for 15 patients [9].

All treatment planning data for IMRT was obtained by inverse planning with commercial treatment-planning systems (Eclipse ver.7.3.10, Varian Medical Systems International Inc., Baden, Switzerland). The IMRT beam arrangements consisted of seven co-planar beams. The prescribed dose for PTV was 70 Gy, and the following dose constraints were set on the organs at risk (OARs): maximum dose for the spinal cord, 45 Gy; maximum dose of the brain stem, 54 Gy; mean dose for at least one parotid gland, 26 Gy, although both parotid glands were tried to spare. Detailed dose constraints for IMRT planning used at our institution are described in Table 2.

Table 2
The objective parameters used in IMRT optimization.

Target and risk organs	Dose constraints
PTV	D_{95} = 100% (prescription dose 70 Gy)
	$V_{110\%}$ < 10% of PTV
	D_{max} < 120%
	D_{mean} < 105%
Organs at risk	
Brain (PRV)	D_{max} < 63 Gy
Brain stem (PRV)	D_{max} < 54 Gy
Spinal cord (PRV)	D_{max} < 45 Gy
Optic nerve	D_{max} < 54 Gy
Amphiblestrode	D_{mean} < 35 Gy
Lens	D_{max} < 6 Gy
Inner/middle ear	D_{mean} < 45 Gy
Oral cavity	D_{max} < 54 Gy
Larynx	D_{mean} < 45 Gy
Parotid gland (at least one)	D_{mean} < 26 Gy
Non-specific region	D_{max} < 70 Gy

Abbreviations: PTV, planning target volume; PRV, planning organ at risk volume; D_{max}, maximum dose; D_{mean}, mean dose; D_{95}, dose to the 95% of the volume; $V_{110\%}$, Volume (%) of receiving 110% of the prescription dose.

Method of analysis

To eliminate interobserver variability, re-contouring of OARs and target volumes was performed by a single observer (TN) and validated by a single medical doctor (YN). The spinal cord was outlined without margin between the first and sixth cervical vertebra level. Parotid glands were also outlined without margin. Utilizing PET–CT findings, the primary tumors and the largest metastatic lymph node were re-contoured without margin as gross tumor volume-p (GTV-p) and GTV-n, respectively.

IMRT plans were defined as follows: Plan-1 was the actual initial IMRT plan applied to CT-1. Plan-2 was the actual boost IMRT plan on CT-2. In addition, a Plan-3, in which the initial IMRT plan was transferred to CT2 based on carefully matched Isocenter and bony alignment, was made for this study. Dose distributions of these plans were recalculated to obtain dose-volume histograms (DVHs) of re-contoured target volumes and OARs. No optimization was performed for Plans-1, 2, and 3 after re-contouring.

The changes in volume, distance and dose were analyzed for each patient. Comparisons of these parameters on Plan-1, Plan-2 and Plan-3 were analyzed by Mann–Whitney–Wilcoxon tests.

Volumes of GTVs and bilateral parotid glands were compared between CT-1 and CT-2 with a paired samples analysis. To quantify the positional shifts of the parotid glands, we calculated the distance from the surface of the parotid glands or the retromandibular vein in the parotid glands to the midline on the slice with the largest parotid gland area.

Dosimetric parameters such as D_{mean}, D_{98}, and D_2 were evaluated for Plan-1, Plan-2, and Plan-3. D_{98}, and D_2 were doses to the 98% and 2% of the volume, respectively. For each IMRT plan, DVHs were calculated for GTVs and critical risk organs. Plan-3 was compared to Plan-1 to evaluate the effects of anatomic changes on dosimetric outcomes. The replanning effects for dosimetric outcomes were compared for Plan-2 and Plan-3. Dose parameters were calculated for a total prescribed dose of 70 Gy for each plan. In addition, D_{mean} (sum) of the bilateral parotid glands was calculated for each patient as follows.

$$D_{mean}(\text{sum}) = D_{mean}(\text{Plan-1}) \times (\text{initial plan dose})/70 + D_{mean}(\text{Plan-2}) \times (\text{boost plan dose})/70$$

After the end of IMRT, loco-regional control and distant progression was evaluated every 3–4 months for more than 5 years by clinical examination, laryngo-pharyngeal fiberscopy, and every 6 months by head and neck MRI or CT scan, as well as thoraco-abdominal CT scan.

Late toxicities were graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. Xerostomia was scored prospectively and recorded in the clinical chart every 3–4 months. The attending physicians (YN and TS) asked patients to follow dietary alterations and the need for a water bottle every 3–4 months, and the best grade at 12–24 months after the start of IMRT was used as an end-point.

Results

Fig. 1(a–c) shows the volume changes in GTVs and parotid glands between CT-1 and CT-2. The mean volumes of GTV-p and GTV-n on CT-2 reached 37.1 ± 23.5% and 47.6 ± 36.8% compared with CT-1, respectively ($p = 0.002$ and $p = 0.081$). The volume of parotid glands also decreased to 81.9 ± 12.4% of the initial volume with significant difference ($p < 0.0001$). The lateral surface of the parotid glands shifted medially with an average of 4.2 ± 2.9 mm ($p < 0.0001$) on CT-2. The retromandibular vein in parotid glands shifted medially with an average of 2.4 ± 3.3 mm ($p = 0.00002$).

Table 3 shows dose parameters calculated for a total prescribed dose of 70 Gy for each plan. D_{means} of parotid glands in Plan-1, Plan-2 and Plan-3 were 25.4 Gy, 20.0 Gy and 30.3 Gy per 70 Gy, respectively. In addition, the average D_{mean} (sum) of the bilateral parotid glands was 23.9 ± 2.6 Gy. According to the anatomical change, D_{mean} of the parotid glands increased significantly between Plan-1 and Plan-3 (5.0 ± 5.1 Gy; 119.9%, $p < 0.0001$). D_{mean} of the parotid glands significantly reduced in Plan-2 compared with Plan-3 (10.3 ± 3.6 Gy; 66.0%, $p < 0.0001$).

There was no statistically significant difference in the D_{mean} of the spinal cord. D_2 values of the spinal cord were 37.2 Gy, 36.7 Gy and 39.1 Gy per 70 Gy, respectively. The increase in the D_2 of spinal cord was statistically significant at Plan-3 compared to Plan-1 (1.9 ± 2.0 Gy; 105.4%, $p = 0.0003$). The increase in D_2 of the spinal cord was correlated with the volume loss of GTV-p (Spearman's correlation coefficient 0.91). D_2 of the spinal cord could be reduced by Plan-2 compared with Plan-3 (2.4 ± 5.2 Gy; 93.9%, $p = 0.0507$) with marginal significance. Between Plan-1 and Plan-3, there was a slight but significant increase in D_{mean} and D_{98} of GTV-p (0.6 ± 0.7 Gy; $p = 0.0007$, 0.8 ± 0.6 Gy; $p < 0.0001$). There were no significant dose changes in D_{mean} and D_{98} of GTV-n.

Fig. 2 shows Plan-1 on CT-1 (a) and the same plan on CT-2 (Plan-3) (b) for nasopharyngeal cancer. The body size on CT-2 has shrunk, and the GTV (shown in pink) has apparently regressed. The parotid glands and spinal cord were included in the high dose region.

The median follow-up period was 57 months (range, 8–78 months). Grade of xerostomia 1–2 years after the start of IMRT could be evaluated for 15 patients. There were 12 patients with grade 0 and 3 patients with grade 1 (Table 1). No patient complained of grade 2 xerostomia in this cohort after 1–2 years. D_{mean} (sum) of parotid glands for the 12 patients with grade 0 and 3 patients with grade 1 were 24.1 ± 1.9 Gy (21.6–27.8) and 21.9 ± 4.7 Gy (17.5–26.8), respectively.

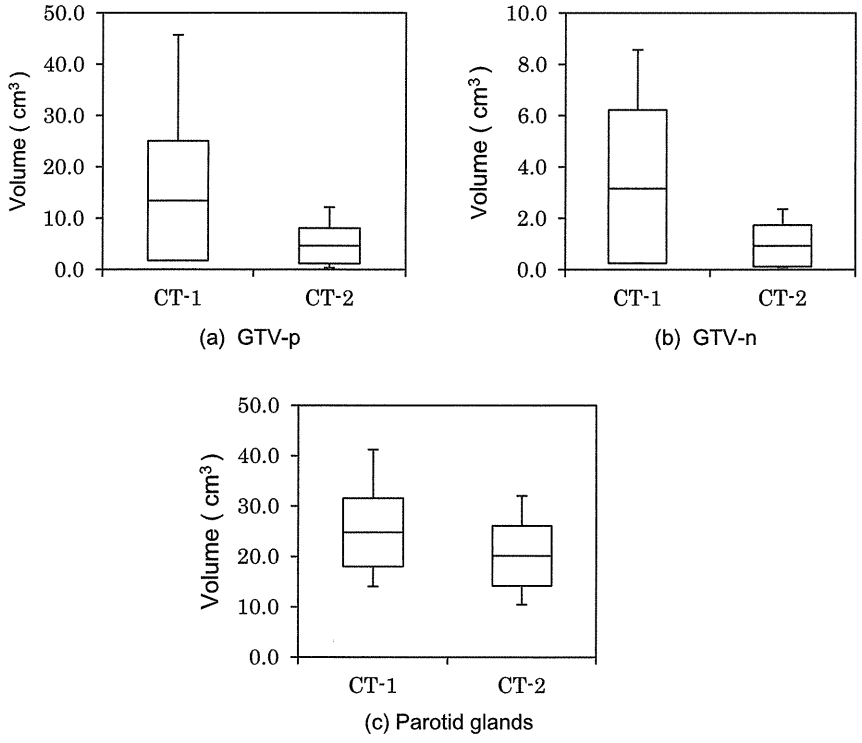

Fig. 1. (a–c). Volume changes of GTV and parotid glands between CT-1 and CT-2. The box represents standard deviation (SD), and the horizontal line in the box represents the mean of the volumes. The bar represents the range of the volumes.

Table 3
Dose parameters calculated for a total prescribed dose of 70 Gy for each plan.

	Index	Plan-1	Plan-2	Plan-3	Plan-3–Plan-1		Plan-3–Plan-2	
		Ave. ± SD	Ave. ± SD	Ave. ± SD	Ave. ± SD	*p* Value	Ave. ± SD	*p* Value
GTV-p	D_{mean} (Gy)	73.2 ± 0.8	72.7 ± 0.7	73.8 ± 0.7	0.6 ± 0.7	0.0007	1.1 ± 0.8	<0.0001
	D_{98} (Gy)	71.4 ± 0.8	71.5 ± 0.7	72.1 ± 0.9	0.8 ± 0.6	<0.0001	0.7 ± 0.6	0.0003
GTV-n	D_{mean} (Gy)	74.3 ± 1.6	73.8 ± 0.5	74.3 ± 1.7	0.0 ± 1.5	0.9600	0.5 ± 1.2	0.3270
	D_{98} (Gy)	72.8 ± 1.7	72.8 ± 0.8	72.6 ± 1.5	-0.2 ± 2.2	0.8150	-0.3 ± 1.5	0.6650
Parotid glands	D_{mean} (Gy)	25.4 ± 2.2	20.0 ± 5.5	30.3 ± 5.3	5.00 ± 5.1	<0.0001	10.3 ± 3.6	<0.0001
Spinal cord	D_2 (Gy)	37.2 ± 5.0	36.7 ± 3.9	39.1 ± 5.2	1.9 ± 2.0	0.0003	2.4 ± 5.2	0.0507

Abbreviations: GTV-p = the volume of primary gross tumor; GTV-n = the volume of maximum metastatic lymph node; D_{mean} = mean dose; D_{98} = dose to the 98% of the volume; D_2 = dose to 2% of the volume.
Plan-1 = initial treatment plan applied on CT-1; Plan-2 = boost treatment plan on CT-2; Plan-3 = the original plan with the initial treatment plan transferred to the same anatomical position of CT-1 on CT-2.

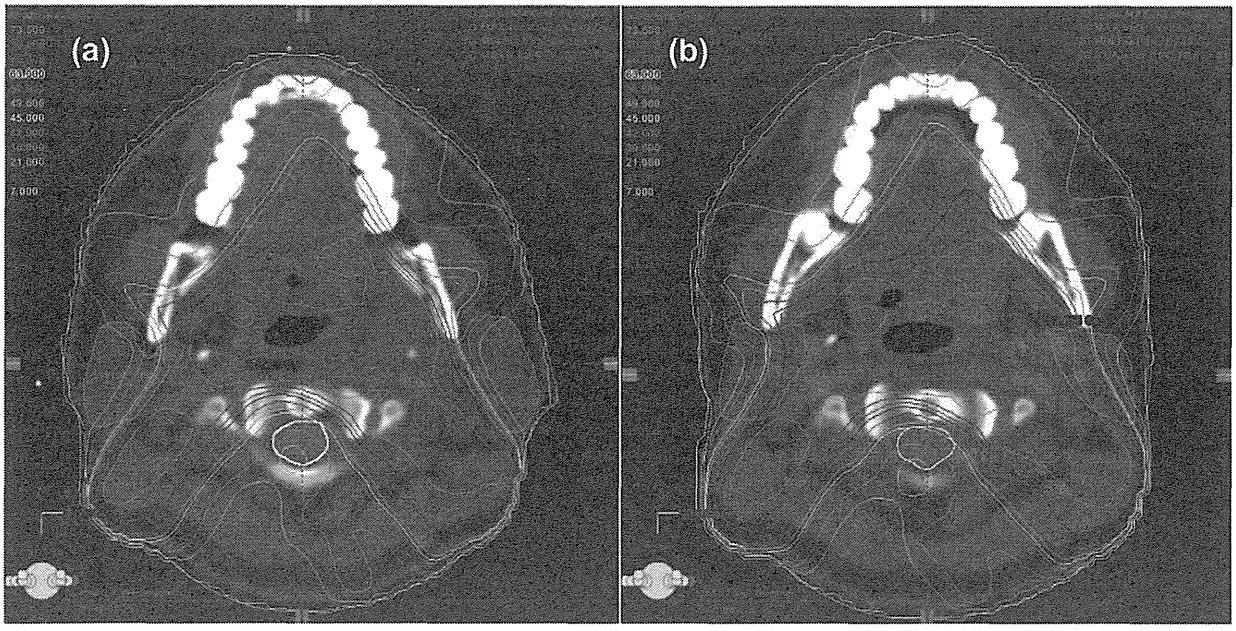

Fig. 2. (a) Dose distribution of the initial IMRT plan on CT-1 (Plan-1) for a patient with nasopharyngeal cancer. (b) Dose distribution of the same plan on CT-2 (Plan-3). The body size on CT-2 shrank, and the parotid glands shifted medially. A 30 Gy iso-dose line (pink) shifted to the middle of the parotid glands (orange).

Loco-regional control rates for patients with NPC and OPC/HPC were 100% and 50%, respectively. Loco-regional recurrences were noted in one patient with HPC and four patients with OPC, although no marginal recurrences were noted (Table 1).

Discussion

Dosimetric and clinical results of our adaptive RT scheme for a two-step IMRT method for head and neck cancers were analyzed in the present study. Although there are many studies on dosimetric changes during IMRT [10–12], a few studies revealed the dosimetric changes and the clinical outcome of adaptive RT [4]. Schwartz et al. [4] performed a prospective study of adaptive RT simultaneous integrated boost (SIB) method for 22 patients with head and neck cancer, and demonstrated that one or two adaptive replanning could provide dosimetric and clinical benefit. Although one replanning was necessary for all patients, second replanning was necessary for 36% (8/22) of the patients. As the significant anatomical changes occurred during 3–4 weeks of treatment [4,5], at least one replanning (two-step) seems necessary for head and neck cancer. The advantage of a sequential two-step method compared with replanning of a SIB method [4,12] may be that the irradiated volume can be reduced in the second step boost IMRT.

Several studies have demonstrated anatomical changes during IMRT with concurrent chemotherapy for head and neck cancer [5–7,10,11]. Similar anatomical and volume changes were noted in the present study, and the position of the parotid glands shifted medially with an average of 4.2 mm. The mean volumes of the GTV-p and parotid glands on CT-2 obtained after 3–4 weeks of IMRT reached 37.1% and 81.9% respectively, compared with CT-1 with significant difference. If replanning was not performed, the parotid glands shifted toward a high dose region (Fig. 2).

In terms of dosimetric changes according to the change in body surface contour and positional changes of target and risk organs for head and neck cancer, significant changes in maximum dose of the spinal cord and D_{50} (dose to 50% of the volume) of the parotid glands were reported by Ahn et al. [10]. They concluded a need for adaptive replanning for head and neck IMRT. In the present study, the mean dose of the parotid glands and D_2 of the spinal cord increased significantly on Plan-3. As a two-step IMRT method can adjust to the anatomical changes in the body surface contour and target and risk organs during IMRT treatment, this method is effective to prevent any increase in the high dose regions of the spinal cord and parotid glands. No patients complained of grade-2 or -3 xerostomia 1–2 years after IMRT. In three prospective studies on one-step IMRT using a SIB method, incidences of grade 2

or worse xerostomia at 1–2 years were reported 16.1%, 29.0%, and 39.3%, respectively [2,13,14]. Thus, our initial clinical results suggest that a two-step IMRT may be effective for preventing xerostomia.

As patients with locally advanced NPC frequently appeared with large neck lymph node swelling and as both primary tumors and neck lymph nodes regress rapidly with RT, a two-step IMRT method is especially desirable for locally advanced NPC. In fact, good loco-regional control was obtained for NPC in the present study.

In conclusion, the dosimetric advantage of a two-step IMRT method was shown for patients with head and neck cancer treated with concurrent chemotherapy. This two-step IMRT method as an adaptive RT scheme could adapt to changes in body contour, target volumes and risk organs during IMRT.

Conflict of Interest

None.

Acknowledgments

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Long-term Follow-up of a Randomized Phase II Study of Cisplatin/5-FU Concurrent Chemoradiotherapy for Esophageal Cancer (KROSG0101/JROSG021)

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Objective: Long-term survival and late toxicities of a randomized Phase II study of chemoradiotherapy for esophageal cancer were analyzed.
Methods: Eligible patients were <75 years old and performance status 0–2, and had Stages II–IVA esophageal cancer. For arm A (short-term infusion), cisplatin 70 mg/m^2 Days 1 and 29 and 5-fluorouracil 700 mg/m^2 Days 1–5 and 29–33 were given concurrently with radiotherapy of 60 Gy/30 fr/7 weeks (1 week split). For arm B (protracted infusion), cisplatin 7 mg/m^2 Days 1–5, 8–12, 29–33 and 36–40, and 5-fluorouracil 250 mg/m^2 Days 1–14 and 29–42 were given with the same radiotherapy. Two cycles of consolidation cisplatin/5-fluorouracil chemotherapy were given to both arms.
Results: Between 2001 and 2006, 91 patients were enrolled; 46 were randomized to arm A, and 45 to arm B. The 2- and 5-year overall survival rates for arm A were 46 and 35% (95% confidence interval: 22–48%), while those for arm B were 44 and 22% (11–35%), respectively. Excluding four patients with early death, seven (17%) patients in arm A and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicities were cardiac or pleural toxicities. Patients with severe late toxicities often had coexistent hypothyroidism. There were three patients with a secondary malignancy possibly related to treatment.
Conclusions: Low-dose protracted infusion chemotherapy with radiotherapy is not superior to full-dose short-term infusion chemotherapy with radiotherapy for esophageal cancer. Late toxicities, including cardiac and pleural toxicities, hypothyroidism and secondary malignancy, should be carefully monitored.

Key words: esophageal cancer – chemoradiotherapy – late toxicities – hypothyroidism – secondary malignancy

INTRODUCTION

For esophageal cancer, a significant improvement in local control and overall survival was achieved with concurrent chemoradiotherapy (CRT) as compared with radiotherapy (RT) alone (1–3). To improve these results, a Phase III trial comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with 5-fluorouracil (5-FU)/cisplatin was conducted (4). In the INT0123 trial, the high-dose arm did not offer a survival benefit compared with the standard dose arm (4). Thus, at present, four cycles of full dose 5-FU/cisplatin combined with 50 Gy of RT is the standard CRT regimen for esophageal cancer in the USA.

Several investigators including ourselves also showed promising clinical results using low-dose protracted infusion chemotherapy (CT) combined with full dose RT of 60–66 Gy for locally advanced esophageal squamous cell carcinomas (5–10). A low-dose protracted infusion of 5-FU or 5-FU plus cisplatin was proposed to reduce the acute toxicities due to concurrent CRT (8,10). In addition, to obtain maximum radiosensitization by CT, daily administration of low-dose protracted CT combined with RT may be better than full dose short-term CT plus RT. When this protocol was started, low-dose protracted infusion CT combined with full dose RT of 60–66 Gy was popular for locally advanced esophageal squamous cell carcinomas in Japan (11).

To test the above hypothesis, this randomized Phase II study was conducted to compare the relative toxicity and efficacy of combining full dose short-term CT (arm A) or low-dose protracted CT (arm B) with RT for esophageal cancer (12). The primary endpoint of the study was the 2-year overall survival rate. In the initial report, the 2-year overall survival rates for arms A and B were 46 and 44%, respectively, without significant difference (12). However, the survival curve of arm A was slightly higher than that of arm B after 2 years, with 5-year survival rates of 35 and 24%, respectively. As all patients could be followed up for more than 5 years after randomization, the long-term survival rate and late toxicities of the trial were re-analyzed in this report.

PATIENTS AND METHODS

Investigational Design

This randomized Phase II multicenter study was started by the Kyoto Radiation Oncology Study Group (KROSG), and joined subsequently by the Japanese Radiation Oncology Study Group (JROSG). The protocol (KROSG0101/JROSG021) was approved by the institutional review boards or ethics committees of all participating institutions, and written informed consent was obtained before entry into the study. The details of the protocol have been published elsewhere (12).

Eligibility Criteria and Treatment Protocol

Inclusion criteria were histologically confirmed esophageal squamous cell carcinoma or adenocarcinoma of Stage II–IVA (UICC 1997). Only patients with no prior therapy, age <75 years, performance status of 0–2, and adequate bone marrow, hepatic and renal function were eligible. Multiple esophageal tumors were also eligible, but tumors with fistula were excluded.

All eligible patients were randomly assigned either to arm A (full dose short-term CT) or arm B (low-dose protracted CT) by customized randomization software; patients were stratified according to tumor length (≤ 6 vs. >6 cm), clinical stage (Stage IIA, IIB vs. Stage III, IVA) and institution.

Two courses of concurrent CT were combined with RT of 60 Gy/30 fractions/7 weeks (1 week split at the fourth week). A 6–15 MV X-ray was used. The daily fractional dose of RT was 2 Gy administered 5 days a week. The primary tumor and involved lymph nodes of ≥ 0.5 cm in the shortest diameter on computed tomography represented the gross tumor volume (GTV). The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2) including the GTV with a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm). CTV1 for cervical, upper, and middle thoracic esophageal cancer included the GTV with a margin plus the supraclavicular and mediastinal lymph nodal areas (T-shaped field). For cervical esophageal cancer, lower mediastinal lymph nodal areas were excluded from CTV1. For tumors originating in the lower thoracic esophagus, CTV1 included the GTV with a margin plus the mediastinal and perigastric/celiac lymph nodal areas (I-shaped field).

For both CTV1 and CTV2, a margin (lateral and anterior/posterior directions 0.5 cm; cranio-caudal direction 1 cm) was added to make planning target volume 1 and 2 (PTV1,2). In addition, leaf margins for PTV1,2 of 0.5–0.8 mm were added. RT doses were specified in the center of the target volume and calculated with lung inhomogenous correction.

Two cycles of CT were delivered concurrently with RT for both arms. For arm A, cisplatin 70 mg/m^2 (Day 1) was delivered via 2 h intravenous infusion (IV), and 5-FU 700 mg/m^2/day was administered as a continuous IV (Days 1–5). For arm B, cisplatin 7 mg/m^2 (Days 1–5 and Days 8–12) was delivered 1 h IV, and 5-FU 250 mg/m^2/day was administered as continuous IV (Days 1–14). For arm B, RT was administered within 1 h after the administration of cisplatin. The total dose of CT was the same for the two arms. This schedule was repeated twice every 4 weeks concurrently with RT. For both arms, two cycles of consolidation CT with cisplatin 70 mg/m^2 (Day 1) and 5-FU 700 mg/m^2/day (Days 1–4) were given after CRT as the protocol.

Follow-up

Locoregional recurrence and distant metastasis were evaluated by barium swallow, upper gastrointestinal endoscopy, and thoraco-abdominal computed tomography scan at

3–6 month intervals after initial evaluation of tumor response. When tumor progression or recurrence was noted, salvage treatment was mandatory for the attending physicians.

Late toxicities observed after 4 months of the start of treatment was graded once a year according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 2.0), because the CTC for Adverse Events version 3.0 was not available in 2001. Maximum grade scored in the follow-up period was recorded for each patient. Although hypothyroidism was scored once a year, periodical thyroid function tests were not mandatory in the protocol. In terms of secondary malignancy, only malignancies that appeared more than 3 years after the randomization in or near the RT field were recorded.

Endpoints

The primary endpoint of the study was the 2-year overall survival rate. Secondary endpoints were overall survival curves, local control curves, acute and late toxicities and the compliance rate of the protocol. When four cycles of CT and 60 Gy of RT could be given as the protocol, the patient was regarded as being in full compliance with the protocol. When two cycles of CT and 60 Gy of RT could be given concurrently, the patient was regarded as being in partial compliance with the protocol. As the concurrent phase of CRT is a major part of the protocol, when at least two cycles of CT and 60 Gy of RT could be given concurrently (full compliance and partial compliance), patients were regarded as per protocol set.

Statistical Analysis

The probability of survival was estimated using the Kaplan–Meier method with statistical significance assessed by the log-rank test. Data were analyzed according to the intent-to-treat principle. Survival was calculated from the date of randomization. Overall survival considered deaths due to any cause. Local control considered any local or regional tumor progression within CTV1 which received 40 Gy or more. When patients died of distant metastasis or other disease without loco-regional progression, local control was censored. Relationships between hypothyroidism and RT fields or other late toxicities were examined by the χ^2 test with Yates' correction.

RESULTS

From December 2001 to June 2006, 91 patients were registered. Forty-six patients were randomly assigned to arm A, and 45 to arm B (Fig. 1). As of June 2011, 71 patients had died, and 20 patients were alive. The follow-up period for the living patients ranged from 59 to 114 months with a median of 83 months. Table 1 shows the characteristics of the 91 patients and treatment parameters according to each treatment arm. There were no significant differences in patient characteristics or treatment parameters between the two arms. The planned dose of 60 Gy was delivered to 88 patients (97%), while RT was terminated at 30 Gy for three patients. When patients with full and partial compliance were combined as per the protocol set, the rate per protocol in arm A (41/46; 89%) was significantly higher than that in arm B (32/45; 71%) ($P = 0.031$).

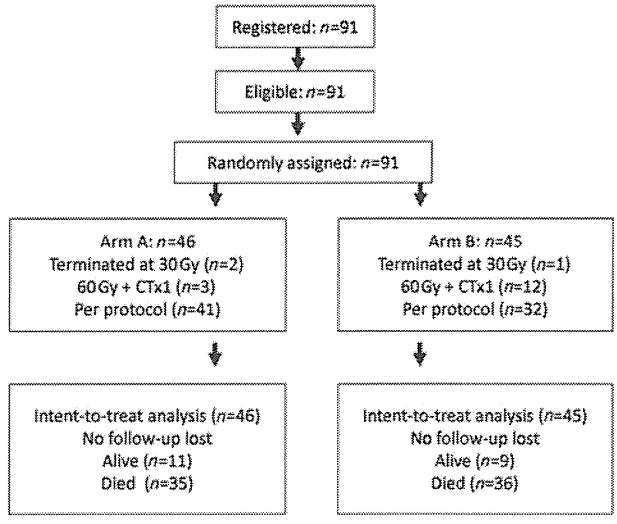

Figure 1. Flow diagram of the patients registered.

Table 1. Characteristics of patients and treatment parameters according to treatment arm (intention-to-treat analysis)

Arm	A ($n = 46$)	B ($n = 45$)
Age (median)	45–74 (63)	48–74 (63)
Male/female	41/5	41/4
PS: 0/1/2	23/20/3	22/21/2
Histology; Sq/Ade	45/1	45/0
Primary site		
Ce/Ut/Mt/Lt	6/13/15/12	4/15/19/7
Length of the tumor		
≤6 cm/>6 cm	23/23 (2–12 cm)	21/24 (1–19 cm)
TNM stage (UICC 1997)		
T1/2/3/4	4/7/14/21	4/9/13/19
N0/1	8/38	9/36
St 2/3/4a	11/30/5	11/27/7
Initial RT field		
T-field	38	38
I-field	8	7

PS, performance status; Sq, squamous cell carcinoma; Ade, adenocarcinoma; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; RT, radiotherapy; TNM, tumor node metastasis; UICC, International Union Against Cancer.

All 91 patients were evaluated in terms of survival based on the intent-to-treat principle. Figure 2 shows the overall survival curves for the two arms. The 2- and 5-year survival rates for arm A were 46% [95% confidence interval (CI): 31–59%] and 35% (95% CI: 22–48%), respectively. Those for arm B were 44% (95% CI: 30–58%) and 22% (95% CI: 11–35%), respectively. There was no significant difference between the overall survival curves.

Figure 3 shows the local control curves for both arms. The 2- and 5-year local control rates for arm A were 38% (95% CI: 24–52%) and 30% (95% CI: 17– 44%), while those for arm B were 34% (95% CI: 21–48%) and 21% (95% CI: 11–35%), respectively. There were no significant differences between the two curves. When residual or recurrent tumors were detected after 60 Gy of CRT, appropriate treatment was chosen by the attending physicians, and salvage surgery was performed for 16 patients. For 12 patients (6 patients in arm A and 6 in arm B), potentially curative resection was achieved, while non-curative resection was achieved in 4 patients (2 patients in arm A and 2 in arm B).

Late toxicities associated with CRT were scored for 87 patients excluding 4 patients who died within 4 months (Table 2). The follow-up period ranged from 4.5 to 114 months (median; 19.5 months). There were no significant differences in late toxicities between the two arms. Seven (17%) patients in arm A and eight (18%) in arm B showed late toxicities of Grade 3 or more. Most of the toxicities were cardiac or pleural toxicities. Five patients showed Grade 4 toxicities including pericardial effusion, pleural effusion and cardiac infarction. Notably, most patients with severe late toxicities had coexistent hypothyroidism. Table 3 shows the relationship between hypothyroidism and RT fields or other late toxicities in 41 patients who survived

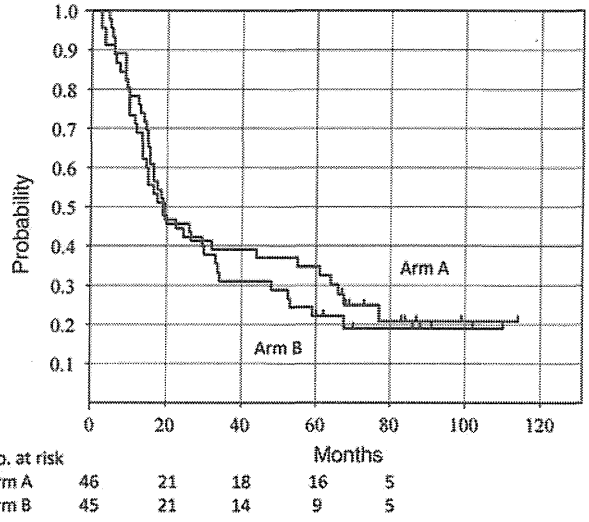

Figure 2. Intent-to-treat analysis of overall survival curves for arm A and arm B.

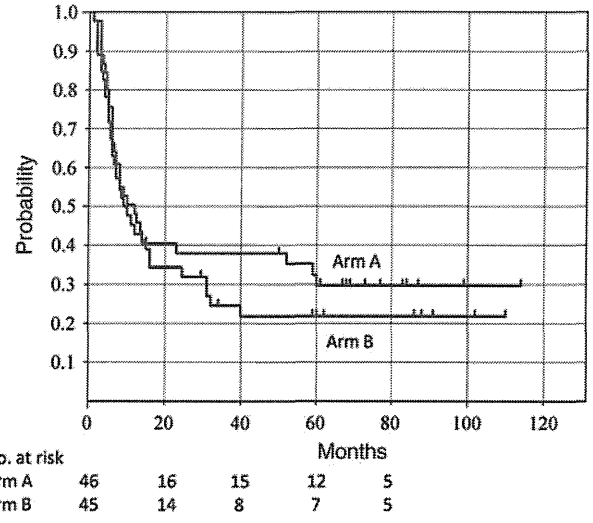

Figure 3. Intent-to-treat analysis of local control curves for arm A and arm B.

Table 2. Late toxicities according to treatment arm [National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, RTOG/EORTC late radiation morbidity scoring scheme]

Arm	A ($n = 42$)	B ($n = 45$)
Esophagus G2/3/4	1/1/0	2/1/0
Heart G2/3/4	0/3/2	2/1/2
Lung G2/3/4	2/0/0	0/1/0
Pleura G2/3/4[a]	1/3/1	4/2/0
Pneumothorax G2/3/4[a]	1/0/0	0/0/0
Hypothyroid G2/3/4[a]	6/0/0	7/1/0
Kidney G2/3/4[a]	0/0/0	0/1/0
Second cancer G2/3/4/5[a]	0/0/1/1	0/0/1/0
Patient max G2/3/4/5	5/2/4/1	9/5/3/0
Patient max ≥G3	7 (17%)	8 (18%)

Four patients who died within 4 months were excluded from the analysis of late toxicities.
[a]Late toxicities graded according to NCI-CTC version 2.0.

Table 3. Relationship between hypothyroidism and RT fields or other late toxicities in patients who survived more than 24 months

Hypothyroidsm	T-field	I-field	
Grade 0	14	7	
Grade 1	7	0	G0 vs. G1–3; $\chi^2 = 5.86$, $P < 0.05$
Grade 2–3	13	0	G0–1 vs. G2–3; NS
	Other late toxicities		
	Grade 0–1	Grade 2–5	
Grade 0–1	18	10	
Grade 2–3	0	13	$\chi^2 = 12.40$, $P < 0.001$

NS, not significant.

more than 24 months. Hypothyroidism of Grade 1–3 was noted in 20 (49%) of the 41 patients. All of the patients with hypothyroidism (Grade 1–3) were treated with a T-shaped field (neck + mediastinum), and no patient treated with an I-shaped field (mediasinum + perigastric/celiac region) showed hypothyroidism ($P < 005$). All 13 patients with Grade 2–3 hypothyroidism had coexistent other late toxicities of Grade 2 or more, while only 10 of 28 patients with Grade 0–1 hypothyroidism had other late toxicities of Grade 2 or more ($P < 0.001$).

There were three patients with a secondary malignancy possibly related to cancer treatment. One patient in arm A died of acute myelogenous leukemia 77 months after CRT without recurrence of esophageal cancer (Grade 5). In another patient, follicular lymphoma of the duodenum was detected 53 months after CRT. This tumor occurred out of the perigastric RT field, and was treated successfully with CT. In one other patient, early gastric adenocarcinoma was detected out of the RT field 32 months after CRT. This tumor was resected endoscopically. For this patient, lung squamous cell carcinoma (T1N0M0) was detected 96 months after CRT in the irradiated volume of 20 Gy. Curative surgery was performed for this early lung cancer, and this patient showed no evidence of disease up to 110 months after the CRT. In this patient, gastric cancer was not regarded as a secondary malignancy because of the short interval, but the lung cancer that occurred in the RT field 96 months after CRT was regarded as a secondary malignancy.

DISCUSSION

The 5-year minimum follow-up of patients in this analysis is critical for evaluation of long-term survival rates and late toxicities associated with CRT for locally advanced esophageal cancer. Only a few prospective trials on CRT for esophageal cancer reported real long-term survival rates. In the RTOG-8501 trial, the 5-year survival rate of patients treated with 50 Gy CRT was 27% (1,2). In the trial, T4 tumors were not included. In the INT-0123 trial, only overall survival rates within 3 years were reported (4). In the Japan Clinical Oncology Group (JCOG) Phase II study of CRT for resectable esophageal cancer excluding T4 tumors, the 5-year overall survival rate was 37% (13). In arm A, the 5-year overall survival rate was 35% (95% CI: 22–48%), even though 46% of the tumors were T4 disease. Thus, the survival rate in this trial especially for arm A (full dose short-term infusion CT) seems excellent.

In the initial analysis, the survival curve of arm A was slightly higher than that of arm B after 2 years, with 5-year survival rates of 35 and 24%, respectively (12). In the present analysis, the 5-year survival rates were 35 and 22% for arm A and arm B, respectively (Fig. 2). Although the 5-year survival rate was still higher for arm A than for arm B, the difference was not statistically significant. In terms of long-term local control rates, arm A showed a better local control rate than arm B, although this was not significant (Fig. 3). Thus, our initial hypothesis that daily administration of low-dose protracted CT is better than full-dose short-term CT in enhancing radio-sensitization effects was not proved.

Grade 3–5 late toxicities were noted in 17–18% of the patients in this analysis. This rate is much lower than 37% in the 50.4 Gy arm of the INT-0123 or 29% in the CRT arm of RTOG-8501 (2,4). The two trials used the same RTOG morbidity scoring criteria for late toxicities as the present study. Most of the serious late toxicities were cardiac or pleural toxicities, and five patients showed Grade 4 pericardiac and/or pleural effusion. Notably, most patients with severe late toxicities had coexistent hypothyroidism. In the present analysis, a significant correlation was noted between Grade 2–3 hypothyroidism and Grade 2 or more other late toxicities (Table 3). Although pericardiac and pleural effusion are well-known late toxicities associated with CRT for esophageal cancer (9,13–15), no investigators have described the relationship between hypothyroidism and pericardiac and/or pleural effusion. Hypothyroidism was only noted for patients treated with a T-shaped field (neck + mediastinum) after several years of RT, and 14 patients needed thyroid hormone therapy. Hypothyroidism is a well-known late toxicity for head and neck cancer, including cervical esophageal cancer (16–18). However, pericardiac and/or pleural effusion are very rare for head and neck cancer. In the treatment of thoracic esophageal cancer, in addition to thyroid glands, the heart and pleura were also irradiated. Thus, the degree of pericardial or pleural effusion may be enhanced by coexistent hypothyroidism.

As a serious late toxicity, secondary malignancies possibly related to cancer treatment were noted in three patients. Although there are several case reports on therapy-related leukemia following definitive CRT for esophageal cancer (19,20), therapy-related solid tumors following CRT for esophageal cancer have not been reported. Acute myelogenous leukemia was noted 77 months after CRT, follicular lymphoma of the duodenum 53 months after CRT and lung squamous cell carcinoma 96 months after CRT. Because a lung tumor was detected 96 months after CRT in the irradiated volume of 20 Gy, the tumor was considered to be a therapy-related tumor. In the present study, two of the three secondary malignancies could be treated curatively. Careful follow-up examinations after 5 years of CRT may be necessary to detect multiple primaries, including CRT-induced secondary malignancies.

In conclusion, our results suggest that low-dose protracted infusion CT with RT is not superior to full-dose short-term infusion CT with RT for esophageal cancer. For long-term survivors after CRT for esophageal cancer, late toxicities including cardiac and pleural toxicities, hypothyroidism and secondary malignancies should be carefully monitored.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003: the Japanese Radiation Oncology Study Group (JROSG) Survey

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Abstract
Background To determine the clinical results of radiotherapy (RT) for esophageal cancer in Japan.
Materials and methods A questionnaire-based survey was conducted for esophageal cancer treated by definitive RT between 1999 and 2003. Clinical results of definitive RT for patients were collected from 9 major institutions. Only patients with good performance status (PS 0–2) who received a total dose of 50 Gy or more were included. Patients were classified into three groups: (A) stage I, (B) resectable stages II–III, (C) unresectable stages III–IVA. For group A, all patients treated by RT alone or chemo-radiotherapy (CRT) were included. For groups B and C, only those treated by CRT were included.
Results In total, 167 patients were included in group A, 239 in group B, and 244 in group C. Approximately half of the patients in group A were treated by CRT. The median total RT dose ranged from 60 to 66 Gy. The median and range of the 5-year overall survival rates were 56% (48–83%) for group A, 29% (12–52%) for group B, and 19% (0–31%) for group C, respectively. A wide disparity in overall survival rates was noted among the institutions. A significant correlation between the number of patients treated per year and the 5-year overall survival rate was noted for groups B and C (both $p < 0.05$).
Conclusion Although the overall survival rates for stage I esophageal cancer were excellent, a significant disparity in survival rates was noted among the institutions for stage II–IVA tumors treated by CRT.

Keywords Esophageal cancer · Chemo-radiation therapy · Brachytherapy · National survey

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Introduction

In the treatment of esophageal cancer, significant improvements in local control and overall survival have been achieved with concurrent chemo-radiotherapy (CRT) compared with radiotherapy (RT) alone [1–3]. In a phase III randomized trial (RTOG-8501), four cycles of full-dose 5-FU/cisplatin (FP) combined with 50 Gy of RT was compared with RT alone (64 Gy), and the CRT arm showed a significant improvement in the overall survival rate [1, 2]. To improve these results, a phase III trial (INT-0123) comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with FP was conducted [4]. In the INT-0123 trial, however, the high-dose RT arm did not show a survival benefit compared with the standard-dose RT arm [4]. Therefore, four cycles of full-dose FP combined with 50.4 Gy of RT is the standard CRT regimen for esophageal cancer in the USA.

In Japan, surgical resection has been preferred for resectable esophageal cancer for T1–3N0,1M0 disease (International Union Against Cancer TNM classification; UICC 2002). Until the mid-1990s, many patients treated by CRT had unresectable T4 disease or metastatic cervical lymph nodes (M1-lymph). Even for these locally advanced T4 or M1-lymph esophageal cancers, 2-year overall survival rates of 20–30% have been reported by Japanese investigators using concurrent CRT of 60 Gy [5–7]. Because of the success of concurrent CRT for unresectable esophageal cancer, definitive CRT has been applied for resectable esophageal cancer (T1-3N0,1M0) since the late 1990s in Japan. Although no randomized clinical trials comparing definitive CRT and surgery for resectable esophageal cancer have been reported, clinical results of concurrent CRT for resectable esophageal cancer are very promising [8–10].

For superficial esophageal cancer (T1N0M0), RT alone with or without intraluminal brachytherapy (IBT) is also as effective as concurrent CRT [11–14]. Recently, a phase II clinical trial of concurrent CRT for superficial esophageal cancer with submucosal invasion has been reported by the Japan Clinical Oncology Group (JCOG) [15]. In the trial, 60 Gy of RT was combined with two courses of FP for 72 patients with stage I (T1N0M0) esophageal cancer, and the 4-year overall survival and major relapse-free survival rates were 81 and 68%, respectively. This survival rate is very similar to that of surgery.

In the early 2000s, concurrent CRT became one of the standard treatments for both resectable and unresectable esophageal cancers in Japan [10, 16, 17]. A questionnaire-based national survey on CRT or RT for esophageal cancer was conducted to evaluate the clinical results for esophageal cancer in major Japanese institutions.

Patients and methods

A questionnaire-based survey of RT for esophageal cancer treated definitively between January 1999 and December 2003 was conducted by the Japanese Radiation Oncology Study Group (JROSG). In May 2008, questionnaires on the results of definitive RT for patients with esophageal cancer were collected from 9 major institutions of the JROSG. Only patients with good performance status (PS 0–2) who received a total dose of 50 Gy or more were included. Patients treated by preoperative or postoperative RT (or CRT) were excluded.

Patients were classified into three groups: group A, those with superficial tumors (T1N0M0; stage I); group B, those with resectable tumors (T1N1M0, T2,3N0,1M0; stages II–III); group C, those with unresectable tumors (T4 or M1-lymph; stages III–IVA). For group A, all patients treated definitely by RT or CRT with or without IBT were included. For groups B and C, only those treated by concurrent CRT were included.

Results

Table 1 shows the numbers of patients in the institutions and groups. In total, 650 patients with esophageal cancer treated by definitive RT were included from nine institutions. All but 10 tumors (98.5%) were squamous cell carcinomas. The age of the patients ranged from 35 to 87 years, and the median ages at each institution ranged from 63 to 71 years. The clinical practice of each institution between 1999 and 2003 is also shown in Table 1. Periodic cancer board meetings consisting of radiation oncologists and surgical oncologists were performed at six institutions, and salvage surgery for locally recurrent or persistent esophageal tumors were performed at seven institutions. The median follow-up periods of surviving and censored patients ranged from 42 to 70 months with a median of 56 months.

Table 2 shows the treatment methods in the institutions between 1999 and 2003. For stage I disease (group A), 60 patients (36%) were treated by IBT following external RT. In terms of chemotherapy for stage I disease, 74 patients (44%) were treated by CRT with or without IBT, and 93 patients (56%) were treated by RT with or without IBT. For all institutions, the median total RT dose for CRT ranged from 60 to 66 Gy.

The type of chemotherapy given concurrently with RT differed significantly among the institutions. Full-dose FP was used most frequently, followed by low-dose FP. Various chemotherapy regimens of full-dose FP were included: (1) two cycles of cisplatin 70–80 mg/m^2 (day 1) and 5-FU 700–800 mg/m^2/day administered as continuous