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頭頸部腫瘍に対する強度変調放射線治療の確立と標準化のための臨床研究

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（総括・~~分担~~）研究報告書

頭頸部腫瘍に対する強度変調放射線治療の確立と標準化のための臨床研究

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研究要旨

強度変調放射線治療(IMRT)は、最新の高精度照射法の一つであり、晩期障害を低減して局所制御を高めることが期待されている。しかしながら、わが国では標準的なIMRT照射法は確立しておらず、その有効性と安全性を明らかにした多施設臨床試験もわが国ではまだなされていない。本研究では、症例ごとの個別化が重要で標準化が困難な頭頸部腫瘍を対象に、原発部位別に3つの臨床試験を行うことによってIMRTの有効性と安全性を評価することを目的とする。

平成23年5月から「上咽頭癌に対する強度変調放射線治療（IMRT）の多施設共同第II相臨床試験（JCOG 1015)」の症例登録を開始し、平成26年2月までに58例が登録された。平成25年度は年間予定数を越える23例の登録が行えた。放射線治療の品質管理体制は、JCOG1015におけるファントム測定と全登録例の治療計画のレビューを通して既に構築できている。平成25年1月に日本放射線腫瘍研究グループ（JROSG）で、「頸部食道癌に対するIMRTを用いた化学放射線療法の多施設共同第II相臨床試験(JROSG 12-1)」が承認され、同年2月から症例登録がはじまり、平成25年度には6例/44例の症例が登録された。また、「T1-2N0-1M0中咽頭癌に対する強度変調放射線治療（IMRT）の多施設共同非ランダム化検証的試験（JCOG1208)」プロトコールコンセプトは、平成24年9月JCOG運営委員会にて承認され、平成25年11月JCOGプロトコール審査委員会に提出し、現在最終審査中で、平成25年度内の承認を目指している。

IMRTは通常照射法では頭頸部腫瘍患者のQOLを落としていた唾液腺障害も低減でき、有効性を保ったままで、これまで以上にQOLのよいがん治療法となることが期待される。本研究に参加する施設は、大学病院もしくはがん診療連携拠点病院であり、本研究で得られたIMRTの品質保証と実施手順は全国各地での安全かつ効果的な頭頸部腫瘍IMRTの基準となり、わが国での頭頸部IMRT照射法の標準化・均てん化に有益であると考えられる。研究成果の一つとして、本研究で実施するIMRTのSIB法とtwo-step法は、「放射線治療計画ガイドライン2012年版」に新たに記載された。

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A．研究目的

強度変調放射線治療(IMRT)は、最新の高精度照射法の一つであり、晩期障害を低減して局所制御を高めることが期待されている。しかしながら、わが国ではIMRTの線量評価法、線量分割法、治療計画法など各施設が独自の方法で行い、標準的なIMRT照射法は確立しておらず、その有効性と安全性を明らかにした多施設臨床試験もわが国ではまだなされていない。本研究では、症例ごとの個別化が重要で標準化が困難な頭頸部腫瘍を対象にIMRTの有効性と安全性を評価することを目的とする。

IMRTは通常照射法では頭頸部がん患者のQOLを落としていた唾液腺障害も低減でき、有効性を保ったままで、これまで以上にQOLのよいがん治療法となることが期待される。現状では限られた施設でしか頭頸部腫瘍に対するIMRTは行われていないが、本研究で実施する3つの第II相試験で得られた結果およびノウハウは、今後わが国での頭頸部IMRTの参考・指針になると考えられる。以上より、本研究はわが国での頭頸部IMRT照射法の標準化・均てん化に有益であると考えられる。

B．研究方法

平成23年5月から「上咽頭癌に対する強度変調放射線治療（IMRT）の多施設共同第II相臨床試験（JCOG1015）」の症例登録を開始した。本研究の目的は、臨床病期II～IVB期（UICC第7版）の上咽頭癌患者に対してIMRTを化学放射線療法として用いることの有効性と安全性を、多施設共同臨床試験において評価する。Primary endpoint：全適格例の3年全生存

割合

Secondary endpoints： 3 年無増悪生存割合、3 年局所領域無増悪生存割合、増悪形式、治療完遂割合、Grade 2 以上の口内乾燥発生割合（1 年、2 年、3 年時点）、有害事象発生割合

適格条件：組織学的に診断された II～IVB 期の上咽頭癌、20 歳以上 75 歳以下、PS0-1、主要臓器機能が保持されている、患者本人からの文書での同意など。

治療： 放射線療法：Two-step 法（治療中に治療計画を変更する）IMRT で 1 回 2Gy、1 日 1 回、週 5 回、計 35 回、総線量 70Gy まで照射し、同時化学療法は CDDP 80mg/m2, day1 を 3 週ごとに 3 コース、その後補助化学療法：5FU 700mg/m2, day1-5, CDDP 70mg/m2, day1 を 4 週ごとに 3 コース行う。

本臨床試験における品質管理・品質保証として、参加施設に放射線治療計画の線量分布計算精度の第三者評価を義務づけ、登録開始前に複数の模擬症例を用いて IMRT 治療計画の事前練習（ドライラン）を実施することにより施設間差を最小化した。また、Image-guided Therapy QA Center の ITC remote review tool を用いて、研究事務局で全例の治療計画と線量分布を確認している。

IMRT を用いた simultaneous integrated boost(SIB) 法（部位により異なる 1 回線量と総線量を照射する）による頸部食道癌プロトコールの対象、治療内容（処方線量、化学療法）を決定した。西村班と日本放射線腫瘍研究グループ（JROSG）消化器委員会の合同試験とすることとし、JROSG12-1 として平成 25 年 1 月プロトコール承認された。平成 25 年度は上記 2 つの臨床試験での症例登録を行う。

「T1-2N0-1M0 中咽頭癌に対する強度変調放射線治療（IMRT）の多施設共同非ランダム化検証的試験」のプロトコールを作成した。抗癌剤の併用はなしで、IMRT は Two-step 法にて予防照射線量は 46Gy/23fr、総線量は 70Gy/35fr とする。

（倫理面への配慮）

JCOG1015、JCOG1208、JCOG1008 は、日本臨床腫瘍研究グループ(JCOG)で実施し、JCOG 放射線治療グループの 13 施設以上が参加する。試験が安全に、かつプロトコールに従って実施されているか、データが正確に収集されているかを確認する目的で、年 2 回定期モニタリングを行う。これらを基に、登録の一時中止、治療法の変更などプロトコール改訂の要否を検討する。JCOG のプロトコール審査委員会、効果・安全性評価委員会、監査委員会、放射線治療委員会などによる第三者的監視を受けることを通じて、科学性と倫理性の確保に努めている。参加患者の安全性確保については、適格条件やプロトコール治療の中止変更規準を厳しく設けており、試験参加による不利益は最小化される。JCOG1015 は、平成 25 年の中間解析でも試験の継続を認められた。また、日本放射線腫瘍研究グループ（JROSG）で行う JROSG12-1 は、これに準じ、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則を遵守する。

C．研究結果

平成23年5月「上咽頭癌に対する強度変調放射線治療（IMRT）の多施設共同第II相臨床試験（JCOG1015）」の症例登録を開始し、平成26年2月までに58例(77%)の症例が登録された。本研究ではIMRTファントムを参加予定施設に送付、線量測定し、IMRT品質保証のための施設調査を行っている。全13施設で調査完了しており、全施設において計画標的体積（PTV）内の測定点での線量測定値に対する線量計算の相違は±3% 以内で許容範囲であり、症例登録可能施設と認定された。また、ITC remote review toolを用いて、研究事務局で全例の治療計画と線量分布を確認し、IMRTの品質保証を行っている。これまで低Na血症、高尿酸血症、呼吸困難、眼内炎、敗血症など6例の比較的重篤な有害事象が報告され、これらを予期される有害事象に追加、減量規準、休止規準を定め、プロトコール改訂を含む適切な処置を行った。

SIB法IMRTによる頸部食道癌プロトコールは平成25年1月に日本放射線腫瘍研究グループ（JROSG）で、「頸部食道癌に対するIMRTを用いた化学放射線療法の多施設共同第II相臨床試験(JROSG 12-1)」承認され、同年2月から症例登録がはじまった。平成26年2月現在6例/44例の症例が登録された。JCOG1015同様、ファントムでの線量測定とドライラン症例の提示を義務付けている。

「T1-2N0-1M0中咽頭癌に対する強度変調放射線治療（IMRT）の多施設共同第II相試験実施計画書」プロトコールコンセプトは、平成24年9月JCOG運営委員会にて承認された（PC1208）。プロトコールを平成25年11月JCOGプロトコール審査委員会に提出し、現在最終審査中、平成25年度内の承認を目指している。

JCOG頭頸部がんグループで実施中の進行頭頸部腫瘍に対する術後照射臨床試験（JCOG1008）において、IMRTを許容するプロトコール改訂案を提示した。照射法についてはSIB法を用いて３つのリスク領域設定でおこなうこととした。本IMRTプロトコール案に従ったドライランを行った。次年度はプロトコール改訂を行う予定である。

D．考察

頭頸部腫瘍に対する手術では外科的な臓器摘出により嚥下、発声などさまざまな機能が失われ、治療後の患者の生活の質(QOL)は著しく下がる。一方、放射線治療は臓器とその機能を温存できるため頭頸部腫瘍に対して特に有用とされてきた。しかし、通常照射法では80%～90%の患者にgrade 2以上（経口摂取に支障あり）の唾液腺障害が生じ患者のQOLを落としていた。IMRTでは、正常唾液腺への照射を回避しつつ腫瘍に対する十分量の照射を行うことが可能であり、2つのランダム化比較試験を含めgrade 2以上の唾液腺障害を20%～30%に有意に低減できており、QOLのよい治療法となることが期待される。

IMRTは先進医療を経て平成20年度から、頭頸部腫瘍、中枢神経腫瘍、前立腺癌を対象に保険収載された。このうち、解剖学的複雑性のため治療の標準化が困難な頭頸部腫瘍では、各施設が独自の方法で治療しており、このままの現状で普

及が進めば、数年後には辺縁再発や予期せぬ晩期障害の発生などの不利益が患者に頻発する可能性が危惧される。

「がん診療提供体制の在り方に関するワーキンググループ報告書(以下、WG 報告書)」（平成２５年８月１日）には、地域がん診療連携拠点病院の診療体制において、IMRT は集約化し効果的な配置が必要との記載がある。本研究に参加する施設は、すべて大学病院あるいはがん診療連携拠点病院であり、本研究で得られた IMRT の品質保証と実施手順は全国各地での安全かつ効果的な頭頸部腫瘍 IMRT の基準となる。さらに、それぞれの地域での関連施設への連携、展開が期待される。研究成果の一つとして、本研究で実施する IMRT の SIB 法と two-step 法は、「放射線治療計画ガイドライン 2012 年版」に新たに記載された。また、本研究では、放射線治療の品質管理において医学物理士の果たす役割が大きく、WG 報告書においても拠点病院に必要な人材とされている医学物理士や放射線治療専門放射線技師などのスタッフ増につながることが期待される。

以上、本研究で実施する臨床試験で得られた結果およびノウハウに基づいて照射法の最適化を行うことによって、わが国での頭頸部腫瘍 IMRT の標準化・均てん化が期待される。

Ｅ．結論

本研究には IMRT を先行実施している主要施設が参加し、臨床試験における放射線治療の品質管理・品質保証の体制を持つ JCOG 放射線治療グループで行うことが特徴である。本研究を継続することによってさまざまな頭頸部腫瘍の根治照射および術後照射に対して、two-step 法および SIB 法 IMRT の有効性と安全性の評価と標準化を図ることが可能である。

Ｆ．健康危険情報

JCOG1015 においては、これまで予期されない grade 3,4 有害事象が 2 例、予期される grade 4 有害事象が 4 例報告され、プロトコールに従って JCOG 効果・安全性委員会に報告し、プロトコール改訂を含む適切な処置をとった。JROSG 12-1 では、これまで重篤な有害事象は報告されていない。

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

研究成果の刊行に関する一覧

1) Nishi T, Nishimura Y, Shibata T, Tamura M, Nishigaito N, Okumura M. Volume and dosimetric changes and initial clinical experience of a two-step adaptive intensity modulated radiation therapy (IMRT) scheme for head and neck cancer. Radiother Oncol 106:85-89, 2013

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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.

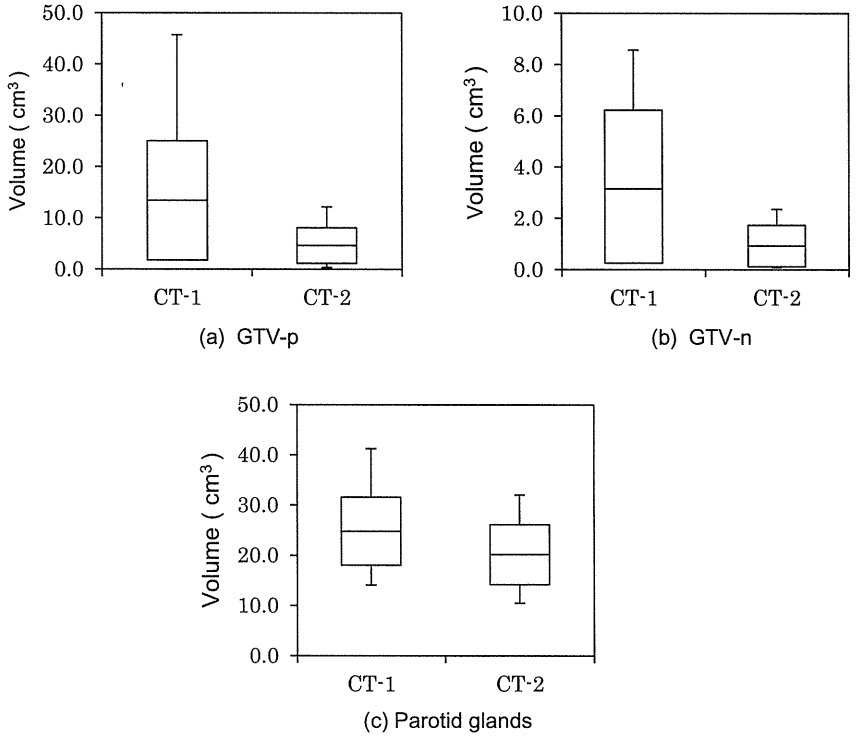

Fig. 1. (a–c). Volume changes of GTV and parotid glands between CT-1 and CT-2. The box represents standard deviation (SD), and the horizontal line in the box represents the mean of the volumes. The bar represents the range of the volumes.

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.

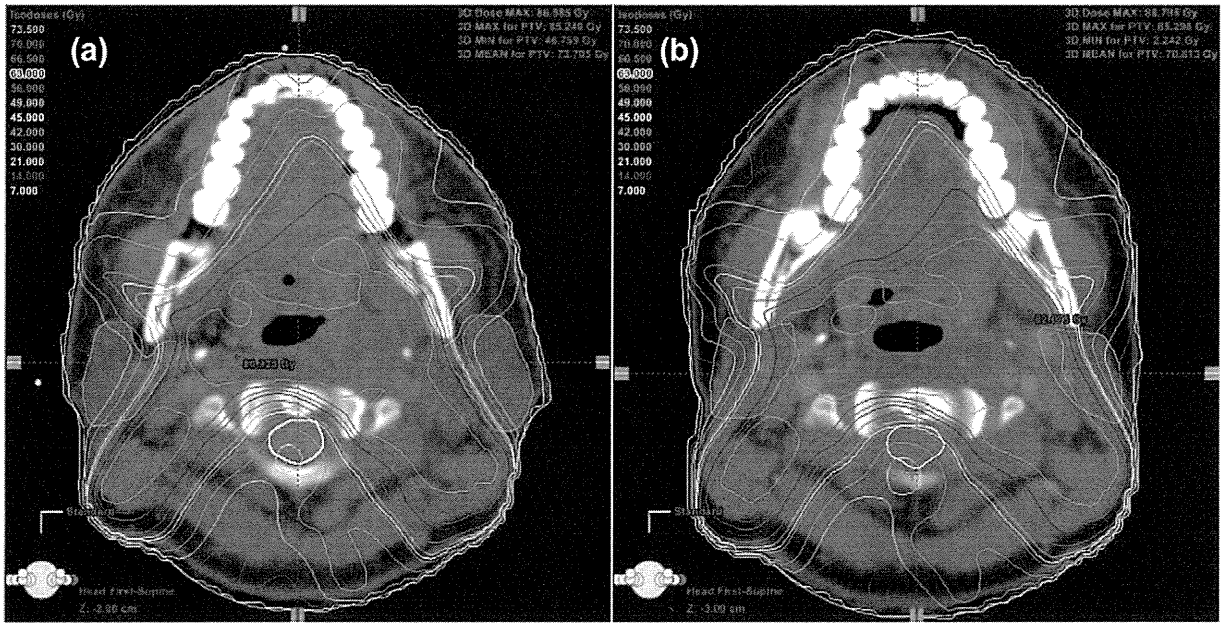

Fig. 2. (a) Dose distribution of the initial IMRT plan on CT-1 (Plan-1) for a patient with nasopharyngeal cancer. (b) Dose distribution of the same plan on CT-2 (Plan-3). The body size on CT-2 shrank, and the parotid glands shifted medially. A 30 Gy iso-dose line (pink) shifted to the middle of the parotid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