Intensity-Modulated Radiation Therapy in Head-and-Neck Cancer, First Report in Thailand

Chawalit Lertbutsayanukul MD*, Chonlakiet Khorprasert MD*,
Kanjana Shotelersuk MD*, Chotika Jumpangern MSc**,
Taweap Sanghangthum MSc**, Sornjarod Oonsiri MSc**,
Isra Israngkul Na Ayuthaya MSc**, Sivalee Suriyapee MEng*,
Winai Wadwongtham MD***, Siripornchai Supanakorn MD***,
Virachai Kerekanjanarong MD***, Prayuth Rojpornpradit MD*

** Division of Radiation Oncology, Department of Radiology,Faculty of Medicine, Chulalongkorn University*
*** Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital*
**** Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University*

Objective: *This is the first report in Thailand to evaluate the efficacy of using intensity-modulated radiotherapy (IMRT) in the primary treatment of head-and-neck cancer.*
Material and Method: *From July 2005 to March 2006, eighteen patients with head and neck cancer were treated with IMRT, fourteen of which were nasopharyngeal cancer. The median age at diagnosis was 52 years (range 23-58 years). The treatment plan composed of two sequential plans for PTV-low risk (50Gy in 25 fractions) and PTV-high risk (20Gy in 10 fractions). Chemotherapy was given to 13 patients with locoregionally advanced disease (stage T3/T4 and N2/3) using cisplatin (n = 3) or carboplatin (n = 10) every 3 weeks during the course of radiation therapy.*
Results: *The median overall treatment time was 49 days (range, 43-57 days), and 77.8 percent of the patients completed 35 fractions within 50 days. The clinical complete response and partial response rates at 3 months after complete radiation were 71.4% and 28.6%, respectively. However, at the median follow-up of 5.6 months, the complete response rate increased to 89%. Treatment break during RT, range from 3 to 7 days, was observed in three patients. All of them received concurrent chemoradiation. No distant metastasis was noted.*
Conclusion: *The authors' experience of using concurrent chemotherapy with IMRT for a cohort of patients with head and neck carcinoma showed a very high rate response rate at early follow-up. Long-term clinical outcome is expected.*

Keywords: *Intensity-modulated radiation therapy, Head neck cancer, IMRT*

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Patients with locoregionally advanced head-and-neck cancer are usually managed with a combination of surgery, chemotherapy, and radiation therapy (RT). Most patients undergoing RT for head and neck cancer are treated with external beam radiation (EBRT) using either a megavoltage linear accelerator or a Cobalt unit. RT can be administered preoperatively or postoperatively or as primary definitive treatment.

Correspondence to : Lertbutsayanukul C, Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: wisutiyano@yahoo.com

Many normal tissues, including the parotid glands, eyes, brain stem, and spinal cord are very close to cancers in the nasopharynx and oropharynx. The dose of radiation delivered to the cancer is limited by tolerance of these normal tissues. Standard RT techniques using three or four radiation beams cannot avoid undesired radiation dose to these normal tissues. Intensity-modulated radiation therapy (IMRT), by virtue of its dosimetric advantage, has gained increasing popularity in the treatment of head-and-neck cancers. It has been enabled by the advent of both improved computer software systems and advance-

ment of the radiation therapy equipments, and is the use of non-uniform radiation beams to achieve conformal dose distributions[1]; thus, enables dose escalation to the planning target volume (PTV) and increases the possibility of local tumor control, as well as reduces dose to normal tissues with subsequent decreased morbidity[2-5].

Despite aggressive combined modality treatment approaches, locoregionally advanced head and neck cancer has a poor prognosis with five-year survival rate below 30 percent[6]. Most deaths are related to locoregionally persistent or recurrent disease. Concurrent chemoradiation is a more attractive strategy in both nasopharyngeal and non-nasopharnygeal carcinoma. Many published studies demonstrated increased local control and overall survival[7-13].

Although, the transition from two dimensional RT to three dimensional RT (3DRT), in particular IMRT, represents a major step forward in the treatment of head-and-neck cancer, the results of IMRT concurrently with chemotherapy are sparse.

In the present report, the authors describe the IMRT treatment technique used concurrently with chemotherapy and report on the early treatment outcome in head-and-neck cancer patients.

Material and Method

Patient databases were used to retrospectively identify all patients presenting with a diagnosis of nasopharyngeal or oropharyngeal carcinoma between July 2005 and March 2006. Patients and tumor characteristics were reviewed, along with treatment variables

Table 1. The definitions of target and organ-at-risk volumes

Volume Definition
1. The Gross Tumor Volume (GTV) is defined as all known gross primary disease (GTV-P) determined from CT, clinical information and endoscopic findings. Grossly positive lymph nodes (GTV-LN) are defined on CT scan as any lymph nodes > 1 cm or nodes less than 1 cm with a necrotic center. Whenever possible, fusion of the MRI images along with the CT images is performed to more accurately define the gross tumor target.
2. The Clinical Target Volume-primary (CTV-P) is defined as the GTV-P plus 5 mm margin in all directions except in situations where the GTV is adjacent to a critical normal tissue, i.e., at the clival-brain stem junction.
3. The Clinical Target Volume-elective lymph node (CTV-ELN) is defined as elective lymph node (level IB-V and retropharyngeal LN). Regarding lymph nodes, CTV-ELN includes the high risk nodes for all cases, namely: a. Upper deep jugular (junctional, parapharyngeal) lumph nodes: bilaterally b. Submandibular lymph nodes (level Ib): bilaterally c. Subdigastric (jugulodigastric)lymph nodes (level II): bilaterally d. Midjugular lymph nodes (level III): bilaterally e. Low jugular and supraclavicular lymph nodes (level IV): bilaterally f. Posterior cervical lymph nodes (level V): bilaterally g. Retropharyngeal lymph nodes: bilaterally h. Submental region (level Ia) would have been included if the submandibular lymph nodes or oral cavity were grossly involved. The lymph node groups at risk are outlined on the treatment planning software according to DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines[15].
4. The Planning Target Volume-high risk (PTV-HR) includes the GTV-P and GTV-LN plus 10 mm margin.
5. The Planning Target Volume-low risk (PTV-LR) includes CTV-P and CTV-ELN plus 5 mm margin. The PTV-LR is a concentric volume that will completely encompass the entire PTV-HR. There should be at least a one mm gap between the PTV and the brain stem. The PTV is truncated 5mm from the skin surface to avoid high dose to the skin.
6. Organs-at-risk (OARs) - Surrounding critical normal structures, including the brain stem, spinal cord, optic nerves, chiasm, parotid glands, mandible, oral cavity, eyes, lens, and glottic larynx should be outlined. The spinal cord contour is expanded,so called “cord expand”, at 5 mm larger in the radial dimension than the spinal cord (i.e., the cord diameter on any given slice is 5 mm larger than the cord itself).

for each patient. All patients were staged using the revised 2002 American Joint Committee on Cancer (AJCC) criteria[14]. All patients were staged by a standard protocol comprising of physical examination, complete ENT examination, computed tomography (CT) of the nasopharynx and neck region, chest radiograph, and liver and bone profiles. All patients had a biopsy to confirm the diagnosis and had a dental evaluation before RT.

Patients with distant metastases at diagnosis and those who had received prior treatment were excluded. Eighteen patients were eligible and served as the subjects of this analysis.

Immobilization and tumor image acquisition

The patient was positioned (in a head-extended position) and immobilized from the head to shoulder using a thermoplastic cast. CT images indexed every 5 mm were obtained, extending from the vertex to 5 cm inferior to the heads of clavicles. The gross tumor volume (GTV), clinical target volume (CTV) and critical normal tissues were outlined on all CT slices in which the structures exist. The volume definitions are demonstrated in Table 1.

Treatment planning

The treatment plan used for each patient was based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the planning target volume (PTV) and organs-at-risk (OARs). Primary tumor and the whole neck were treated by IMRT using nine coplanar beams, separated at 40 apart. An "inverse" planning using computerized optimization (Helios version 7.3.10, Varian, PA) was used. The plan would be accepted if (1) the prescribed dose encompassed at least 95% of the PTV, (2) no more than 10% of the PTV received more than 110% of the prescribed dose, (3) no more than 1% of the target received less than 93% of the prescribed dose, and (4) the maximum dose (Dmax) was below the tolerant limit for each OAR. The photon energy used in the present study was 6 MV. The final dose distribution was calculated using the Eclipse treatment planning system with inhomogeniety correction (Eclipse version 7.2.34, Varian, PA). Treatment was then delivered by dynamic MLC on a Varian linear accelerator (Varian 23EX) equipped with 120-leaf MLC.

Dose Specifications

The treatment plan composed of two phases, the first phase for PTV-low risk (50Gy in 25 fractions) followed by the other for PTV-high risk (20Gy in 10 fractions). Therefore, the total dose of the PTV-high risk was 70 Gy in 35 fractions. Target dose and organs-at-risk dose volume constraint (DVC) are shown on Table 2 and 3, respectively.

Chemotherapy

Chemotherapy was given to 13 patients with locoregionally advanced disease (stage T3/T4 and N2/3) using cisplatin (n = 3) or carboplatin (n = 10) every 3 weeks during the course of RT. Adjuvant chemotherapy was given to 12 patients, including cisplatin in one patient and carboplatin in the others.

Post-treatment assessment included physical examination with complete ENT examination approximately every 3 months in the first 3 years of follow-up, every 6 months in the third to fifth years, and annually

Table 2. Prescription dose of PTV for IMRT planning of the head-and-neck carcinoma (n = 18)

Target volume	Sequential		
	Goal dose (Gy)	Number of Fractions	Dose/fraction (Gy)
PTV-LR	50	25	2
PTV-HR	20	10	2

Table 3. Dose volume constraints of organs-at-risk for IMRT planning of the head-and-neck carcinoma

Organs-at-risk	Dmax* (Gy)	DVC	
		Dose (Gy)	Max Volume
Cord expand	45		
Brain stem	54		
One Parotid gland		22	50%
Optic nerve	54		
Optic chiasm	54		
Eyes	50	22	50%
Lens	6		
Glottis	70	50	50%
Mandible	60	60	50%
Oral cavity	50	35	50%

* Dmax defines as radiation dose encompasses 1% of each organ-at-risk volume except cord expand and brain stem which define as dose encompasses 1-ml volume of cord expand and brain stem

thereafter. A follow-up CT or MRI scan of the nasopharynx and neck was performed to document response and to determine whether the patient was clinically disease free or required further diagnostic biopsy and/or treatment. Clinical response was evaluated using RECIST criteria[16].

Data were presented as mean, median and range or number and percentage.

Results

From July 2005 to March 2006, eighteen patients with head and neck cancer were treated with IMRT, fourteen of which were nasopharyngeal cancer. The median age at diagnosis was 52 years (range 23-58). Table 4 summarizes the patient characteristics. All patients completed IMRT. The median overall treatment time was 49 days (range, 43-57 days), and 77.8 percents of the patients completed 35 fractions within 50 days. Treatment break during RT, range from 3 to 7 days, was observed in three patients. All of them received concurrent chemoradiation.

Dose-volume analysis

Tables 5 and 6 summarize the dose volume histogram statistics for the target volumes and the OARs, respectively. Maximum dose (Dmax) and minimum dose (Dmin) were defined as the dose received by 1% and 99% of the volume concerned and calculated from sum plans. The average Dmax, mean dose, and Dmin delivered were 75.0 Gy, 72.1 Gy, and 68.6 Gy to the PTV-HR, and 74.4 Gy, 63.5 Gy, and 48.2 Gy to the PTV-LR, respectively. On average, the target coverage, defined as the percentage of target volume that received the prescribed dose (V70Gy), was 97.1% for the PTV-HR. Only 0.3% of the PTV-HR and 0.8% of the PTV-LR received less than 95% of the prescribed dose (i.e., cold spots defined as 66.5 Gy for PTV-HR

Table 4. Patient characteristics (n = 18)

Characteristics	No. of patients (%)
Gender	
Male	13 (72.2)
Female	5 (27.8)
Primary	
Nasopharynx	14 (77.8)
Tonsil	2 (11.1)
Base of tongue	1 (5.6)
unknown primary	1 (5.6)
Tumor stage	
T1	6 (33.3)
T2	5 (27.8)
T3	5 (27.8)
T4	1 (5.6)
Tx	1 (5.6)
Nodal stage	
N0	1 (5.6)
N1	8 (44.4)
N2	9 (50.0)
N3	0 (0)
Stage group (AJCC2002)	
I	2 (11.1)
II	5 (27.8)
III	9 (50.0)
IV	2 (11.1)

Table 5. Target DVH statistics (n = 18)

Structure	Variable	Average result (range)
PTV-HR	Volume (cc)	371.0 (41.0-629.0)
	Maximum dose D1% (Gy)	75.0 (68.9-77.4)
	Mean dose (Gy)	72.1 (67.5-74.3)
	Minimum dose D99% (Gy)	68.6 (61.1-73.2)
	V70Gy* (%)	97.1 (94.1-99.9)
	V < 95%** (%)	0.3 (0-2.0)
	V > 110% (%)	0.2 (0-1.7)
PTV-LR	Volume (cc)	968.9 (556.0-1395.0)
	Maximum dose D1% (Gy)	74.4 (64.6-76.5)
	Mean dose (Gy)	63.5 (56.7-67.5)
	Minimum dose D99% (Gy)	48.2 (45.9-53.5)
	V < 95% (%)	0.8 (0-2.3)

* V70 Gy and V >110% define as the percentage of PTV received at least 70 Gy and 110% of the prescribed dose
** V < 95% defiens as the percentage of PTV received less than 95% of prescribed dose

Table 6. Organs-at-risk DVH statistics

Structure	Variable	Average result (range)
Spinal cord	Maximum dose D1cc (Gy)	40.8 (31.9-49.5)
	V45 Gy* (cc)	0.6 (0-5.7)
Brainstem	Maximum dose D1cc (Gy)	47.5 (36.1-54.4)
	V54 Gy (cc)	0.2 (0-1.2)
Optic nerve	Maximum dose D1cc (Gy)	28.3 (2.2-55.8)
	V54 Gy (cc)	0.1 (0-1.1)
Ipsilateral parotid	Mean dose (Gy)	39.7 (25.8-61.1)
	Median dose D50% (Gy)	35.4 (22.3-61)
Contralateral parotid	Mean dose (Gy)	31.7 (23.5-46.5)
	Median dose D50% (Gy)	27.0 (19.9-48.6)

* V45 Gy (cc) defines as the volume of the organ that received > 45 Gy

and 47.5 Gy for PTV-LR, respectively). Only 0.2% of the PTV-HR received more than 110% of the prescribed dose (i.e., hot spot defined as 77 Gy).

The average brainstem and spinal cord Dmax were 47.5 Gy and 40.8 Gy, respectively. The optic nerve received an average maximum dose of 28.3 Gy. Contralateral parotid gland received less radiation dose than ipsilateral parotid (average median dose of 27 Gy and 35.4 Gy, respectively). Fig. 1 and 2 demonstrate a radiation dose distribution and DVH of one patient, respectively.

Response rate

The clinical complete response and partial response rates at 3 months after completion of RT were 71.4% and 28.6%, respectively. However, at the median follow-up of 5.6 months, the complete response rate increased to 89%. The local control of the primary disease was observed in 94.4%, while the corresponding figure for regional lymph node was 88.9%. Since there were only three patients who had treatment break, it was not possible to observe any difference in local or regional control compared to ones who completed treatment without a break. No distant metastasis was noted. Figure 3 compares pre and post treatment CT images at the level of nasopharynx and lymph nodes.

Discussion

IMRT has gained popularity in the treatment of head-and-neck cancer as study results suggest noteworthy incremental improvements in dose distributions over 3D conformal plans and encouraging early clinical outcomes[2-5]. Similarly, in the current study, the PTV coverage is excellent and the hot spot is only 0.2% of the PTV. There is no hot spot outside the PTV.

The obvious advantage with IMRT is the ability to deliver 70 Gy to the primary tumor, and reduce the dose to the contralateral parotid gland to a median dose of 27 Gy. This should translate into minimal late xerostomia and thus improves the quality of life[17-19]. Eisbruch reported a correlation between parotid salivary flow recovery and mean dose received by the parotid gland[17]. A mean dose threshold of 24 Gy and 26 Gy were required for non-stimulated and stimulated parotid salivary flow, respectively, to recover to at least 25% of baseline flow at 12 months after completion of

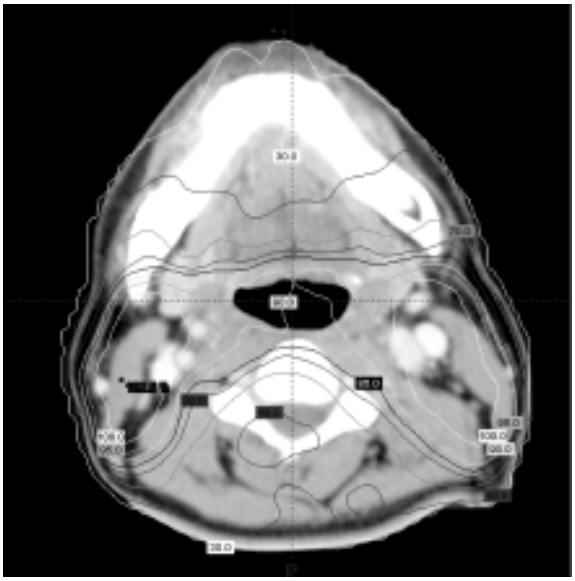

Fig. 1 Radiation dose distribution of one patient

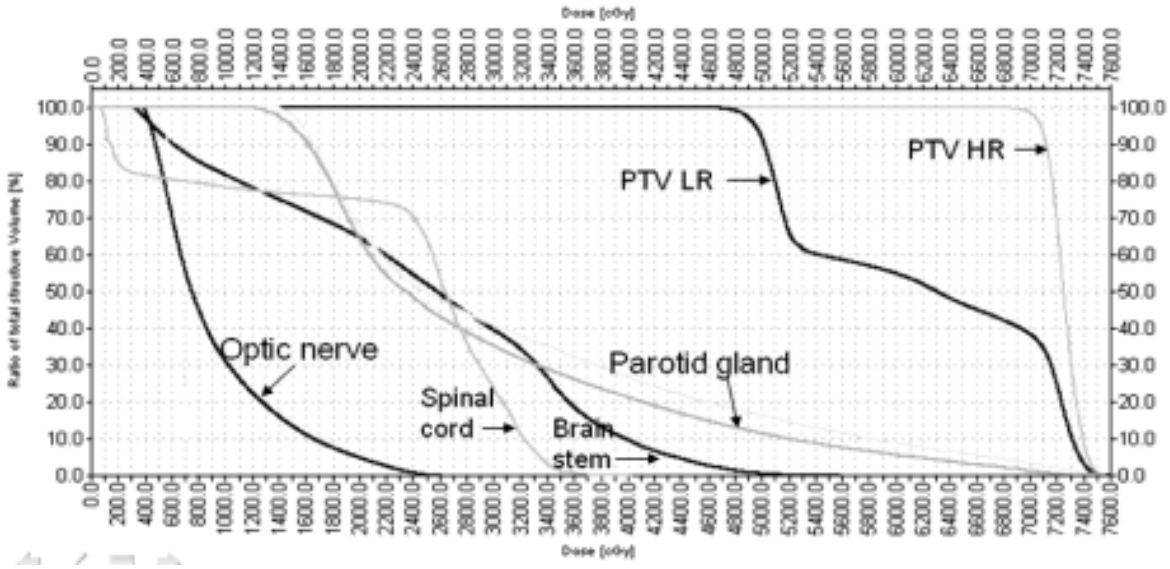

Fig. 2 Dose-volume histograms of the same patient as in Fig. 1

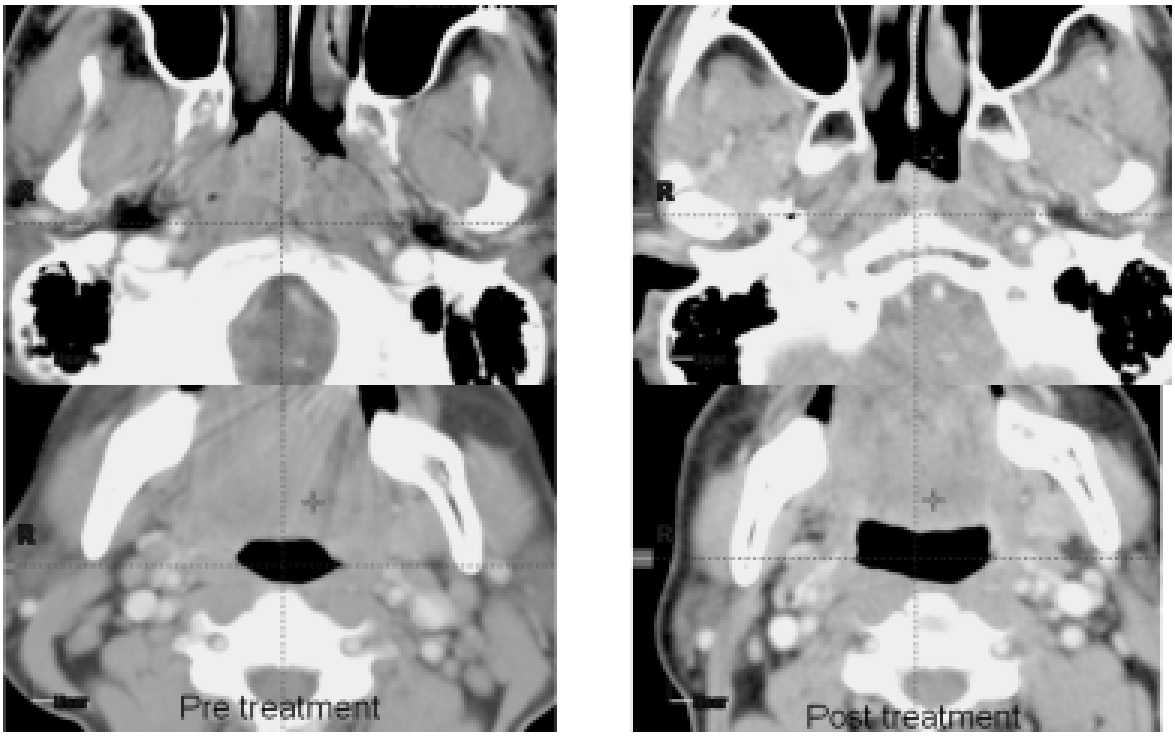

Fig. 3 A comparison of pre and post treatment CT images at the level of nasopharynx and lymph nodes

RT. While Chao predicted a higher threshold dose of 32 Gy for stimulated whole salivary flow[18]. Kwong reported an average mean parotid dose of 38.8 Gy (range, 32.0-46.1 Gy)[19]. Although the mean dose was higher than those reported by Eisbruch and Chao, 60% and 47.1% of patients recovered at least 25% of their baseline stimulated parotid salivary flow and stimulated whole salivary flow at 1 year after completion of RT. The corresponding figures rose to 85.7% and 71.4%, respectively, by 2 years.

Concurrent chemoradiation is used in several cancers, including squamous cell carcinoma of the head and neck to overcome radiation resistance. Chemotherapy can enhance the cytotoxicity of RT and, if given in systemically active doses, may eradicate micrometastatic disease. It has been shown to be better than radiation alone for patients with locally advanced unresectable head neck cancer and nasopharyngeal cancer[7-13]. However, there is no prospective randomized trial that compared IMRT versus concurrent chemotherapy with IMRT.

Wolden reported the update result of IMRT at Memorial Sloan-Kettering Cancer Center [5]. Seventy-four patients with newly diagnosed, non-metastatic nasopharyngeal cancer were treated with IMRT; of these, 69 patients received concurrent and adjuvant platinum-based chemotherapy similar to that in the Intergroup 0099 trial[10]. The 3-year actuarial rate of local control was 91%, and regional control was 93%. Freedom from distant metastases, progression-free survival, and overall survival at 3 years were 78%, 67%, and 83%, respectively. There was 100% local control for stage T1/T2 disease, compared to 83% for T3/T4 disease ($p = 0.01$). These results were the same as that used for 3D treatment in their historical control.

The present study demonstrated that concurrent cisplatin or carboplatin with IMRT was feasible. Minor treatment breaks were observed in only 3 out of 18 patients. The authors' early results showed excellent disease control with IMRT. Nearly 95% of the patients had primary disease controlled, while nearly 90% had regional lymph node controlled. The prescribed dose to PTV-HR was 70 Gy, which was not different from the dose used for conventional treatment, was in accordance with desired dose volume constraint. However, the actual mean dose achieved by IMRT was higher, with an average of 72.1 Gy to PTV-HR and 63.5 Gy to PTV-LR. The higher dose achieved in the PTVs might have contributed to better locoregional control.

The experience with IMRT for nasopharyngeal cancer reported by Lee from the University of California - San Francisco (UCSF) also showed excellent locoregional control, with 4-year local and locoregional control estimates of 97% and 98%, respectively [4]. Most patients had Stage III/IV disease and had received chemoradiotherapy. Patients from USCF received 65-70 Gy to GTV and an additional boost of 5-7 Gy with intracavitary brachytherapy after external beam irradiation. In the present study, the average minimum doses to PTV-HR and PTV-LR were 68.6 and 48.2 Gy, respectively, but no additional boost was given after primary IMRT. The present short-term follow-up demonstrated 89% complete response rate. Long-term local and regional control rates are expected.

Chong recently reported the result of 104 patients who underwent inverse planning IMRT with MIMiC[20]. With median follow-up of 19 months, 3-year actuarial estimates of local progression-free, regional progression-free, and distant metastases-free survivals were 98%, 99%, and 88%, respectively. Their 3-year estimate of overall survival was 86%.

Chao reported the result of IMRT in 430 patients with carcinoma of the oropharynx at the Mallinckrodt Institute of Radiology[21]. There were 260 patients with tonsil primary tumors and 170 patients with tumors arising from the base of the tongue. The median follow-up was 3.9 years. IMRT showed a trend of superior local-regional tumor control.

Obvious disadvantages of IMRT are the initial cost of capital equipment and the increased load on treatment planning time, required by the radiation oncologist and physicist, compared to a conventional conformal RT plan technique. In addition, the IMRT plan needs individualized quality assurance and this process is time-consuming. However, the treatment time required for IMRT is not significantly different to other standard head and neck treatment times, since there is only a single isocenter and the gantry can be controlled from the outside panel.

Conclusion

This is the first report of the result of IMRT in Thailand. The authors' experience of using concurrent chemotherapy with IMRT for a cohort of patients with head and neck carcinoma showed a very high rate of locoregional control at early follow-up. Satisfactory dosimetric sparing of the parotid is observed; this is expected to contribute to improved quality of life. Long-term clinical outcomes are expected. Prospective study of concurrent chemoradiation in locally advanced head and neck cancer is ongoing.

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การรักษามะเร็งศีรษะและลำคอด้วยการฉายรังสีแบบปรับความเข้ม รายงานแรกในประเทศไทย

ชวลิต เลิศบุษยานุกูล, ชลเกียรติ ขอประเสริฐ, กาญจนา โชติเลอศักดิ์, โชติกา จำปาเงิน, ทวีป แสงแห่งธรรม, สรจรส อุณห์ศิริ, อิศรา อิศรางกูร ณ อยุธยา, ศิวลี สุริยาปี, วินัย แวดวงธรรม, ศิริพรชัย ศุภนคร, วีระชัย คีรีกาญจนะรงค์, ประยุทธ์ โรจนพรประดิษฐ์

วัตถุประสงค์*: รายงานนี้เป็นรายงานแรกในประเทศไทยที่ศึกษาถึงประสิทธิภาพในการรักษามะเร็งศีรษะและลำคอด้วยการฉายรังสีแบบปรับความเข้ม*

วัสดุและวิธีการ*: ทำการศึกษาในผู้ป่วยมะเร็งศีรษะและลำคอ 18 ราย ซึ่งได้รับการรักษาด้วยการฉายรังสีแบบปรับความเข้มที่โรงพยาบาลจุฬาลงกรณ์ ระหว่าง เดือน กรกฎาคม พ.ศ. 2548 ถึง มีนาคม พ.ศ. 2549 ในจำนวนนี้มีผู้ป่วยมะเร็งหลังโพรงจมูก 14 ราย มัธยฐานอายุของผู้ป่วยทั้งหมดเท่ากับ 52 ปี (พิสัย 23-58 ปี) การรักษาประกอบด้วยการฉายรังสีแบบปรับความเข้มต่อกัน 2 แผน โดยแผนแรกให้ปริมาณรังสี 50 เกรย์ ใน 25 ครั้งต่อก้อนมะเร็งที่มีความเสี่ยงต่ำ ต่อด้วยแผนที่สองให้ปริมาณรังสี 20 เกรย์ ใน 10 ครั้งต่อก้อนมะเร็งที่มีความเสี่ยงสูง ผู้ป่วย 13 รายที่เป็นมะเร็งศีรษะและลำคอระยะลุกลามเฉพาะที่ ได้รับยาเคมีบำบัดร่วมด้วย โดยมีผู้ป่วย 3 รายได้รับยาซีสพลาติน และ ผู้ป่วย 10 รายได้รับยาคาร์โบพลาตินทุก 3 สัปดาห์ในระหว่างการฉายรังสี*

ผลการศึกษา*: มัธยฐานของระยะเวลาการฉายรังสีแบบปรับความเข้มเท่ากับ 49 วัน (พิสัย 43-57 วัน) ผู้ป่วยร้อยละ 77.8 ได้รับการฉายรังสีครบ 35 ครั้งภายใน 50 วัน เมื่อติดตามผลการรักษาที่ 3 เดือนพบว่าก้อนมะเร็งยุบหมดร้อยละ 71.4 และก้อนมะเร็งยุบกึ่งหนึ่ง ร้อยละ 28.6 และเมื่อติดตามผลการรักษานานขึ้นเป็น 5.6 เดือนพบว่ามีอัตราการยุบหมดเพิ่มขึ้นเป็นร้อยละ 89 พบผู้ป่วยเพียง 3 รายเท่านั้นที่จำเป็นต้องพักการฉายรังสีชั่วคราว (ระหว่าง 3-7 วัน) โดยทั้ง 3 รายได้รับยาเคมีบำบัดควบคู่กับการฉายรังสี ขณะนี้ยังไม่มีรายงานการแพร่กระจายของมะเร็งไปอวัยวะอื่น*

สรุป*: การศึกษานี้ชี้ให้เห็นว่าการรักษามะเร็งศีรษะและลำคอด้วยการฉายรังสีแบบปรับความเข้มมีอัตราการตอบสนองต่อการรักษาดีมาก ในอนาคตจะมีรายงานการติดตามผลการรักษาในระยะยาวต่อไป*