Pattern of failure after adjuvant postoperative radiotherapy in head and neck cancers

รูปแบบการกำเริบในผู้ป่วยมะเร็งศีรษะและลำคอที่ได้รับการฉายรังสีหลังการผ่าตัด

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Abstract

Background: Locoregional recurrence is a predominant failure in locally advanced head and neck cancers despite of multimodality treatment including surgery and adjuvant chemoradiation. Analysis of locoregional failure pattern can contribute to improvement of future treatment.

Objective: To evaluate pattern of failure in head and neck cancers treated with postoperative radiotherapy.

Materials and Methods: Head and neck cancer patients who underwent postoperative radiotherapy in Thammasat hospital from October 2015 to January 2019 were retrospectively reviewed. The site of locoregional recurrence were correlated with previous radiotherapy treatment plan.

Results: Total 49 patients of squamous cell carcinoma head and neck cancers underwent postoperative radiotherapy. Primary were originated from the following subsites; oral cavity 25(51%), oropharynx 1 (2%), larynx 19 (39%), hypopharynx 3 (6%), unknown primary 1 (2%). Pathological staging based on AJCC 7th edition were as followings: 2 were stage I (4%), 2 were stage II (4%), 9 were stage III (18%), 34 were stage IVA (69%), 2 were stage IVB (4%) and none were stage IVC. Pathological risk factors were as followings : 9 positive margins(18%), 17 extracapsular extensions(35%),38 pathological T3 or pT4(78%), 18 pathological N2 or pN3(37%), 21 close margins(43%), nodal disease in level IV or V for primary oral cavity cancer in four patients(16%), 19 lymphovascular invasions (39%) and 18 perineural invasions(37%). Median follow up time was 16 months (range, 2-48 months). There has been disease failure in 12 cases (25%) with eight locoregional failure (16.66%), six distant metastasis (12.5%) and two have synchronous locoregional and distant failure (4.16%). Median time of locoregional failure was 5.5 months (range, 3-26 months). Of eight locoregional failure, six were in-field, one was out-field and one had both in and out-field recurrence. The 2-year cumulative rate of overall survival, progression-free survival, distant metastasis-free survival and locoregional control rate were 64%, 53%, 84% and 74%, respectively.

Conclusion: In-field locoregional failure is the predominant pattern in head and neck cancers treated with adjuvant postoperative radiotherapy.

Keywords: intensity-modulated radiotherapy, patterns of failure, postoperative radiotherapy

บทคัดย่อ

หลักการและเหตุผล: การกำเริบเฉพาะที่เป็นปัญหาที่พบมากในผู้ป่วยมะเร็งศีรษะและลำคอระยะลุกลามเฉพาะที่แม้จะได้รับการรักษาแบบสหวิชาชีพด้วยการผ่าตัดและฉายรังสีร่วมกับเคมีบำบัด การศึกษาวิเคราะห์รูปแบบตำแหน่งการเกิดการกำเริบเฉพาะที่จะสามารถนำไปสู่การพัฒนาแนวทางการรักษาในอนาคตต่อไป

วัตถุประสงค์: เพื่อศึกษารูปแบบการกำเริบในผู้ป่วยมะเร็งศีรษะและลำคอที่ได้รับการรักษาด้วยการฉายรังสีหลังการผ่าตัด

วัสดุและวิธีการ: การทบทวนเวชระเบียนย้อนหลังของผู้ป่วยมะเร็งศีรษะและลำคอที่ได้รับการฉายรังสีหลังการผ่าตัดใน โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ตั้งแต่ตุลาคม 2558 ถึงมกราคม 2562 และทำการเปรียบเทียบตำแหน่งรอยโรคที่กำเริบเฉพาะที่กับแผนการรักษาด้วยการฉายรังสี

ผลการศึกษา: ผู้ป่วยมะเร็งศีรษะและลำคอที่ได้รับการรักษาด้วยการฉายรังสีหลังการผ่าตัด
มีจำนวน 49 ราย มะเร็งศีรษะและลำคอมีต้นกำเนิดมาจากตำแหน่งดังนี้; มะเร็งในช่องปาก 25 ราย (51%), มะเร็งคอหอยส่วนปาก 1 ราย (2%), มะเร็งกล่องเสียง 19 ราย (39%), มะเร็งคอหอยส่วนล่าง 3 ราย (6%) และไม่ทราบต้นกำเนิด 1 ราย (2%) ระยะของโรคแบ่งตามผลพยาธิวิทยาตามรายงานของคณะกรรมการโรคมะเร็งแห่งอเมริกา ฉบับที่ 7 ได้แก่ ระยะที่ I 2 ราย (4%),II 2 ราย (4%), III 9 ราย (18%), IVA 34 ราย (69%), IVB 2 ราย (4%) และไม่พบว่ามีผู้ป่วยในระยะ IVC ปัจจัยเสี่ยงจากผลพยาธิวิทยาที่พบได้แก่ พบเซลล์มะเร็งที่ขอบชิ้นเนื้อ 9 ราย (18%), การลุกลามเนื้อเยื่อข้างเคียงต่อมน้ำเหลือง 17 ราย (35%), ระยะลุกลามของก้อนมะเร็งระยะที่สามหรือสี่ 38 ราย (78%), ระยะลุกลามของต่อมน้ำเหลืองระยะที่สองหรือสาม 18 ราย (37%), พบเซลล์มะเร็งใกล้ขอบชิ้นเนื้อ 21 ราย (43%), การลุกลามของต่อมน้ำเหลืองลำคอระดับที่สี่หรือห้าในมะเร็งช่องปาก 4 ราย (16%), การลุกลามเข้าหลอดเลือดหรือหลอดน้ำเหลือง 19 ราย (39%), การลุกลามเข้าเส้นประสาท 18 ราย (37%) ค่ามัธยฐานของการติดตามการรักษาได้แก่ 16 เดือน (ระหว่าง 2-48 เดือน) พบการกำเริบของโรค 12 ราย (25%) โดยเป็นการกำเริบเฉพาะที่ 8 (16.66%) การแพร่กระจาย 6 ราย (12.5%) โดยมี 2 รายที่พบทั้งการล้มเหลวเฉพาะที่และแพร่กระจายร่วมกัน (4.16%) ค่ามัธยฐานของการกำเริบเฉพาะที่เท่ากับ 5.5 เดือน (ระหว่าง 3-26 เดือน) ในผู้ป่วยจำนวน 8 รายที่กำเริบเฉพาะที่ เป็นการกำเริบภายในขอบเขตการฉายรังสีจำนวน 6 ราย และภาวะล้มเหลวภายนอกขอบเขตการฉายรังสีจำนวน 2 ราย อัตราการรอดชีวิตในระยะเวลา 2 ปีเท่ากับ 64% อัตราการรอดชีวิตโดยไม่มีโรคในระยะเวลา 2 ปีเท่ากับ 53% อัตราการรอดชีวิตโดยไม่มีการแพร่กระจายของโรคในระยะเวลา 2 ปีเท่ากับ 84%, อัตราการควบคุมโรคบริเวณเฉพาะที่ในระยะเวลา 2 ปีเท่ากับ 74%

ข้อสรุป: รูปแบบการกำเริบเฉพาะที่ ในผู้ป่วยมะเร็งศีรษะและลำคอ ที่ได้รับการฉายรังสีหลังการผ่าตัดที่พบมากที่สุดได้แก่ การกำเริบเฉพาะที่ภายในขอบเขตการฉายรังสี

คำสำคัญ: การฉายรังสีแบบปรับความเข้ม, การฉายรังสีหลังการผ่าตัด, รูปแบบการกำเริบ

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Introduction

Multimodality treatment is often applied in locally advanced squamous cell head and neck cancer. Non-nasopharyngeal primary subsites such as oral cavity benefit from upfront surgery [1]. Despite surgical resection of gross disease, recurrence rate is still significant. Adjuvant treatment is incorporated to enhance disease control. Pathological risk factors that warrant postoperative concurrent chemoradiation include positive resection margin or extracapsular spread of disease[2]. While other adverse features as

following; pathological T staging three or four (pT3 or pT4), N staging two or three nodal disease (pN2 or pN3), nodal involvement in level IV or V in primary oral cavity cancer, perineural invasion, or vascular tumor embolism require postoperative radiation alone.[3,4] Role of IMRT were established in nasopharyngeal, oropharyngeal, oral cavity, laryngeal, hypopharyngeal and unknown head-and-neck primary in both definitive[5,6,7] and postoperative[8,9,10] settings. Based on data from locally advanced disease, systemic chemotherapy still proved to be the most optimal choice of concurrent treatment compared to targeted therapy drug [11]. Postoperative treatment subsequently adopted the regimen. However, locoregional recurrence at tumor bed is still the predominant site[12,13]. This study aimed to explore failure pattern of postoperative radiotherapy in head and neck cancers in our institute.

Materials and methods

A retrospective chart review with radiation treatment planning analysis was done in head and neck squamous cell carcinoma patients who underwent postoperative radiotherapy in Thammasat hospital from October 1, 2015 to January 31, 2019.

Multidisciplinary tumor board determined overall treatment plan for each patient. Our general approach is surgery followed by adjuvant treatment for oral cavity cancer. The same approach is also considered in those with locally advanced laryngeal, supraglottic and hypopharyngeal cancer not amenable to laryngeal preservation. Postoperative chemoradiation was given in the patient with pathological positive margin or extracapsular extension of lymph node (ECE). Any of the following pathological risk factors; primary tumor staging three or four (pT3-pT4), nodal staging two or three disease(pN2-pN3), nodal involvement in level IV or V for primary oral cavity cancer, lymphovascular invasion (LVI), perineural invasion (PNI) or close margin warrants postoperative radiation. Classification of stage were initially based on American Joint Committee on Cancer seventh edition (AJCC 7th) but AJCC eighth edition staging was also reported upon availability.

Postoperative radiotherapy started after complete wound healing, generally not exceeding six-week interval. Patient underwent simulation computerized axial tomography. Head, neck and shoulders were immobilized in a supine hyperextended position using a standard perforated thermoplastic head and neck mask supported on a cushion mounted on a carbon fiber board (Overlay Board type-S). A serie of axial images was obtained on a CT simulator (Siemens SOMATOM Definition AS open 20/64) with continuous 3-mm slice thickness. Contour of target tumor and organ at risk was performed by radiation oncologists. Additional deformable image registration with axial MRI T2-weighted FS

and axial contrast-enhanced T1-weighted FS was performed in those with pathological microscopic or macroscopic residual disease. Target delineation is as followed:

• High-risk Clinical Target Volume (HR-CTV): Tumor bed adjacent to the positive margin or extracapsular extension was defined by using surgical clip, imaging and operative note correlated with pre-surgery clinical information. HR-CTV include entire operative bed and adjacent levels of ipsilateral or contralateral involved lymph nodes.

• Low-risk Clinical Target Volume (LR-CTV): The entire operative bed and subclinical ipsilateral and/or contralateral cervical lymph node.

• The CTVs were then expanded with 0.5 centimeters circumferential margin to create planning target volumes (PTVs). Trimming of the PTVs within five millimeters from the skin surface was performed to enable proper dose planning.

Intensity-modulated radiotherapy (IMRT) or Volume modulated arc therapy (VMAT) planning was calculated using Elekta' s Monaco treatment planning system which subsequently treated with Versa HD Linear accelerator.

The prescription dose for Low-Risk Planning Target Volume (LR-PTVs) was 54 Gy in 1.64 Gy per fraction. Simultaneous integrated boost technique was used with the prescribed dose of 59.4 Gy for HR-PTVs or up to 66 Gy in 1.8-2 Gy per fraction in case of positive margin or valid extracapsular extension. For gross residual disease evident upon CT simulation, the prescription dose was increased up to 69.96 Gy in 2.12 Gy per fraction.

Chemotherapy

In patients with pathological risk factors of positive margin and extracapsular extension, postoperative concurrent chemoradiation (CCRT) was the treatment of choice. Platinum-based chemotherapy was prescribed weekly with Cisplatin 40 mg/m² being the first choice. Carboplatin was an alternative choice for those with creatinine clearance less than 60 mL/min.

Outcome measurement

After completed treatment, regular follow-up was scheduled at one month and then every three months during the first year, and once every six months from two to five years. Radiologic examination using CT scan or further MRI if clinically indicated was performed at three months after treatment and every six months or sooner if clinically suspected. Disease failure was determined by combination of clinical examination and radiologic examination, in certain cases and/or pathological evidence. Recurrent disease found within three months after radiotherapy was defined as persistent disease.

Pattern of failure classification

Locoregional failure was evaluated using

diagnostic computed tomography (CT) or magnetic resonance imaging (MRI) images which was co-registered with the radiation treatment plan with rigid registration. Gross persistent or recurrent tumor was contoured as fGTV. We classified the patterns of locoregional failure with the degree correlated within the planning CTVs as follows: 1.In-field recurrence if >95% of fGTV was in HR-or LR-CTV, 2.Marginal-field recurrence if 20-95% of fGTV was in HR-or LR-CTV, 3.Out-field recurrence if less than 20% of fGTV was within HR-or LR-CTV.

Evaluation of adverse events

Evaluation of acute and late side effects was graded according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0. Adverse events recorded in scheduled clinical evaluation during and after radiation treatment were reviewed. Acute side effects as followings: mucositis, dermatitis, weight loss and febrile neutropenia occurred during radiotherapy and within 90 days after completion. Adverse events beyond 90 days after radiation were categorized as late side effects which were reported as followings: xerostomia, dysphagia and skin fibrosis.

Ethics

Protocol was reviewed and data access was approved by the Human Research Ethics Committee of Thammasat university.

Statistics

We performed time to event analysis using Kaplan-Meier method. The overall survival (OS) was from the start date of radiotherapy until death from any cause. Locoregional control (LRC) was from the start date of radiotherapy until local and or regional recurrence. Progression-free survival (PFS) was from the start date of radiotherapy until death or any relevant events including locoregional recurrence or distant metastasis. Distant metastasis free survival (DMFS) was from the start date of radiotherapy until distant metastasis. Patients who died without experiencing any of these events were censored at the time of last follow-up. Cox regression model was used to calculate univariate and multivariate analysis for pathological risk factors that affect outcomes.

Results

Patient characteristics

From October 2015-January 2019, 49 patients of head and neck squamous cell carcinoma underwent postoperative radiotherapy in Thammasat hospital. The patient characteristics are listed in **Table 1**. There were 36 males (73%) and 13 females (27%) with the age ranged from 37 to 87 (median age 61 years) Head and neck cancers were originated from the following primary subsites; 25 oral cavity(51%), one oropharynx(2%), 19 larynx(39%), three hypopharynx(6%), one unknown primary(2%).

Pathological staging based on AJCC 7th edition were as followings: two stage I (4%), two stage II (4%), nine stage III (18%), 34 stage IVA (69%) and two stage IVB (4%). Pathological review based on AJCC 8th was also performed. Data were available in 40 of patients **(Table 2)**. Pathological risk factors were positive margin nine(18%), extracapsular extension 17(35%),pathological T3 or pT4 38(78%), pathological N2 or pN3 18(37%), close margin 21(43%), nodal disease in level IV or V in primary oral cavity cancer four(16%), lymphovascular invasion 19 (39%) and perineural invasion 18(37%).

Table 1. Patient Characteristics

Characteristic		No. of patients	% of total
Sex	Male	36	73
	Female	13	27
Age	50 and below	9	18
	51-60	15	31
	61-70	11	22
	>70	14	29
Primary Site	Oral cavity	25	51
	Oropharynx	1	2
	Larynx	19	39
	Hypopharynx	3	6
	Unknown primary	1	2
Pathological	Positive margin	9	18
Risk Factors	Extracapsular extension	17	35
	pT3 or pT4	38	78
	pN2 or pN3	18	37
	Close margin	21	43
	Lymphovascular invasion	19	39
	Perineural invasion	18	37
	Positive level IV or V node in primary oral cavity cancer	4	8

Table 2. Pathological staging

Pathological staging AJCC 7th				Pathological staging AJCC 8th			
		(N=49)	%			(N=40)	%
T0		1	2	T0		1	3
T1		5	10	T1		0	0
T2		7	14	T2		4	10
T3		12	24	T3		15	38
T4a		23	47	T4a		19	48
T4b		1	2	T4b		1	2
N0		23	47	N0		24	60
N1		8	16	N1		5	13
N2a		3	6	N2a		3	8
N2b		5	10	N2b		3	8
N2c		10	20	N2c		2	5
N3		0	0	N3a		0	0
				N3b		11	28
Stage	I	2	4	Stage	I	0	0
	II	2	4		II	2	5
	III	9	18		III	8	20
	IVA	34	69		IVA	18	45
	IVB	2	4		IVB	12	30
	IVC	0	0		IVC	0	0

Treatment

Postoperative radiation alone was given to 21 patients (43%), while 28 patients (57%) underwent postoperative concurrent chemoradiation. In postoperative CCRT, chemotherapy was given one to seven cycles with the average of six cycles. There were 22 patients received Cisplatin and six patients received Carboplatin. Median time from surgery to the start of radiotherapy was 43 days (range, 33-90 days). Dose of radiation was 50.4 to 69.96 Gray (median 66 Gray). Out of 49 patients, there were 48 radiation plans

available for review. Radiation planning was IMRT in 44 cases (92%) and VMAT in four cases (8%). Course of radiation treatment ranged from 14 to 71 days (average 47 days).

Survival outcomes

Forty-eight out of total 49 patients were available for post treatment follow-up with 36 patients (75%) being alive at last follow-up visits. Median follow- up time was 16 months (range,2-48 months) There has been disease failure in 12 cases (25%) with eight locoregional failure (16.66%), six distant metastases (12.5%) and two synchronous locoregional and distant failure (4.16%). Three locoregional recurrence (6%) were detected within the first three month of follow-up thus they were defined as persistent disease although no postoperative gross residual lesions were detected in two of them prior to radiation. The 2-year cumulative rate of OS, PFS, DMFS and LRC rate is 64%, 53%, 84% and 74% respectively **(Figure 1)**.

Out of 25 patients in oral cavity primary subgroup, there were seven disease failure (28%) which five were locoregional failure (20%). Four cases were in-field recurrence and one was out-field recurrence. The 2-year rate of OS, PFS, DMFS and LRC in oral cavity cancer is 57%, 49%,81% and 64% respectively.

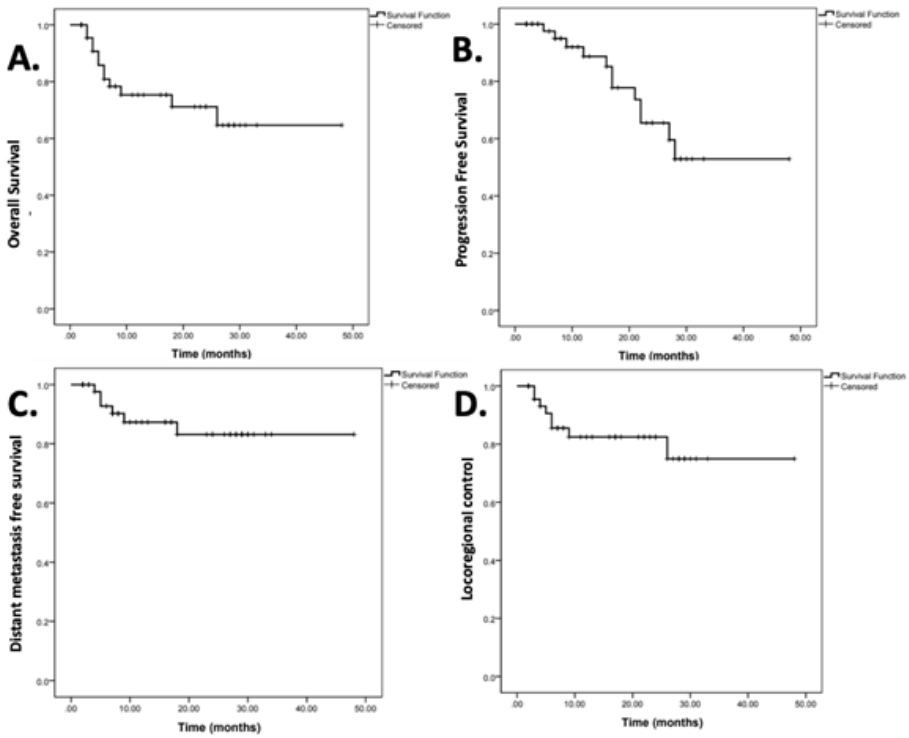

Figure 1. Treatment outcomes using the Kaplan-Meier method.

Univariate analysis identified pathological risk factors favorably affecting overall survival as following: N2-N3 nodal disease (hazard ratio [HR] 0.26, 95% CI 0.08-0.84, P=0.02), nodal involvement in level IV or V for primary oral cavity cancer (HR 0.21, 95% CI 0.06-0.75, P=0.02). Comparison between those who received radiation dose up to 66-69.96 Gy to those who received less than 66 Gy showed no statistical difference in term of disease failure. (HR 0.71, 95% CI 0.24-2.14, P=0.55). Univariate analysis is shown in **Table 3**.

Table3. Univariate analyses of different pathological risk factors and treatment outcomes.

	OS			PFS			DMFS			LRC		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
PSM	0.46	0.12-1.73	0.25	0.42	0.11-1.58	0.20	0.87	0.10-7.52	0.90	0.48	0.10-2.42	0.38
ECE	1.01	0.32-3.19	0.99	1.08	0.32-3.59	0.91	1.09	0.20-6.01	0.92	1.63	0.33-8.14	0.55
pT3-pT4	0.72	0.16-3.31	0.68	0.99	0.27-3.70	0.99	3.21	0.65-15.90	0.15	0.45	0.06-3.69	0.46
pN2-pN3	0.26	0.08-0.84	*0.02*	0.62	0.2-1.98	0.42	0.49	0.1-2.45	0.39	0.75	0.18-3.19	0.70
Level IV-V	0.21	0.06-0.75	*0.02*	0.45	0.13-1.50	0.19	0.52	0.09-2.84	0.45	0.71	0.14-3.57	0.68
LVI	2.06	0.55-7.64	0.28	3.56	0.78-16.27	0.10	48.47	0.06-40728	0.26	2	0.40-9.95	0.39
PNI	0.94	0.3-2.96	0.91	2.05	0.55-7.60	0.28	53.91	0.07-40855	0.24	1.08	0.26-4.54	0.92
CM	1.81	0.54-6.07	0.34	1.52	0.45-5.11	0.50	3.37	0.39-29	0.27	1.27	0.30-5.43	0.74

Abbreviations: OS=overall survival, PFS=progression free survival, DMFS=distant metastasis free survival, LRC=locoregional control, HR=hazard ratio, CI=confidence interval, PSM=positive surgical margin, ECE=extracapsular extension, pT3-pT4=pathological T staging three or four, pN2-pN3=pathological N staging two or three nodal disease, Level IV-V=nodal involvement in level IV or V in primary oral cavity cancer, LVI=lymphovascular invasion, PNI=perineural invasion, CM=close margin.

Disease failure

Median time of locoregional failure was 5.5 months (range, 3-26 months). Of eight locoregional failure, six were in-field, one was out-field and one had both in and out-field recurrence. Pattern of locoregional recurrence is shown in **Figure 2**. Among patients with in-field recurrence, three of recurrent tumor were within HR-CTV, two were out of HR-CTV but within LR-PTV and one had both synchronous lesions.

In one out of two out-field recurrence, patient had synchronous in-field lesion in which appeared within HR-CTV. There were six patients who had distant metastasis at median follow-up of six months (range, 4-18 months) in which two of them had locoregional failure before developed distant metastasis. Details of locoregional recurrence shown in **Table 4** can be further clarified as following: Case one had received 69.96 Gy radiation due to gross residual tumor. The more appropriate option is re-resection which was determined impossible at the time. The patient subsequently developed in-field failure at tumor bed. Case two and four had in-field locoregional failure at both high dose area given to tumor bed and low dose area given to nodal area. **Figure 3A** demonstrates case three which later developed locoregional failure out of field at right intraparotid node which was initially negative on diagnostic CT. Case five and seven had local failure within low dose nodal region before distant metastasis was later identified in case five. Case six had risk factors of left nodal ECE, close margin, LVI and PNI. The patient then completed radiation treatment of 54 Gy with additional boost to left neck and tumor bed

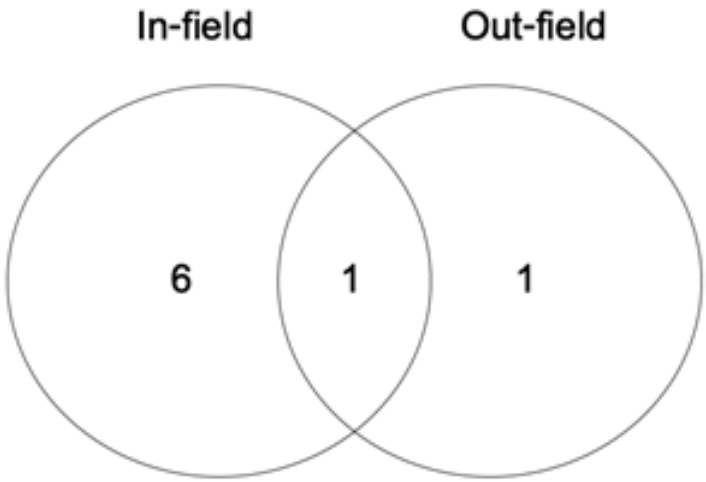

Figure 2. Venn's diagram illustrated pattern of locoregional failure.

Table 4. Profile of locoregional recurrence.

Patient	Primary site	Pathological stage	AJCC 7th	Pathological risk factor	Radiation dose	Weekly concurrent chemotherapy	Pattern of recurrence	Time (months)	Recurrent site	Synchronus recurrence
1	Oral cavity	pT4aN0	IVA	PSM, pT3-T4,PNI	69.96/59.4/54 Gy in 33 Fx	Carboplatin x7	In-field	2	Tumor bed	-
2	Oral cavity	pT4aN1	IVA	PSM,ECE, pT3-T4,PNI	68/54 Gy in 33 Fx	Carboplatin x3	In-field	4	Tumor bed, Level II	-
3	Oral cavity	pT4aN0	IVA	CM,pT3-T4	60/54 Gy in 30 Fx	-	Out-field	3	Level II periparotid nodal area	-
4	Oral cavity	pT4aN0	IVA	pT3-T4	60/54 Gy in 30 Fx	-	In-field	7	Tumor bed, Level II nodal area	Distant metastsis
5	Oral cavity	pT4aN2c	IVA	pT3-T4, pN2-N3	60/54 Gy in 30 Fx	-	In-field	3	Level IV nodal area	Distant metastsis
6	Larynx	pT3 N2b	IVA	ECE,CM, pT3-T4,pN2-N3,LVI,PNI	66/54 Gy in 33 Fx	-	Out-field	4	Level II periparotid, IV nodal area, subdermal	In-fie
7	Larynx	pT3N2b	IVA	pT3-T4,pN2-N3,LVI,PNI	60/54 Gy in 30 Fx	-	In-field	1	Level II nodal area	-
8	Larynx	pT4aN1	IVA	CM,pT3-T4,LVI	60/54 Gy in 30 Fx	-	In-field	8	Tumor bed	-

Abbreviations: PSM=positive surgical margin, pT3-pT4=pathological T staging three or four, PNI=perineural invasion, ECE=extracapsular extension, CM=close margin, pN2-pN3=pathological N staging two or three nodal disease, LVI=lymphovascular invasion.

to 66 Gy. Locoregional recurrence was later found at left level IV which was within 66 Gy treatment volume and at following out-field locations; floor of mouth invading into subcutaneous layer and left periparotid region which was negative in the diagnostic CT imaging. The latter site was demonstrated in **Figure 3B.** In case eight, there was tumor recurrence at tumor bed within high dose area which is demonstrated in **Figure 4**.

Postoperatively before adjuvant radiation, gross residual tumors were detected in eight cases which total radiation dose of 69.96 Gy were prescribed to gross tumor. There was no increased risk of disease failure in the group with postoperative gross residual tumor. (HR 2.12, 95% CI 0.66-6.78, P=0.21)

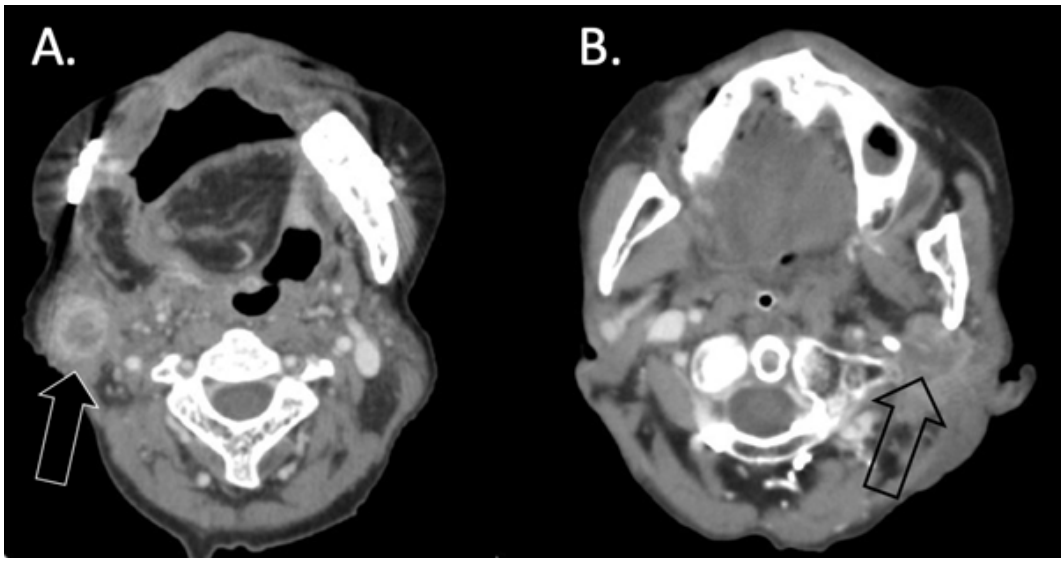

Figure 3. Out-field recurrence at periparotid nodal region.

These are follow-up CT images that detected locoregional failure.

A 64-year old male diagnosed of lower gum cancer underwent wide excision with partial glossectomy with right modified radical neck dissection and left selective neck dissection level I-III with right pectoralis muscle flap. The pathological stage was pT4N0M0 with close margin at primary tumor bed. Adjuvant radiation treatment of 60/54 Gy in 30 fractions was then given. There was a locoregional at right periparotid region which was not present in the diagnostic CT imaging.

Figure 3A. The arrow shows locoregional recurrence at right periparotid region.

A 79 year-old male diagnosed of supraglottic cancer underwent total laryngectomy with left extended neck dissection and right selective neck dissection level II-IV. The pathological stage was pT3N2bM0 with risk factors of left nodal ECE, close margin, LVI and PNI. The patient then completed radiation treatment of 54 Gy with boost to left neck and tumor bed to 66 Gy. Locoregional recurrence was later found at left level IV which was within 66 Gy treatment volume and at out-field locations; floor of mouth invading into subcutaneous layer and left periparotid region which were negative in the diagnostic CT imaging.

Figure 3B. The transparent arrow shows locoregional recurrence at left periparotid region.

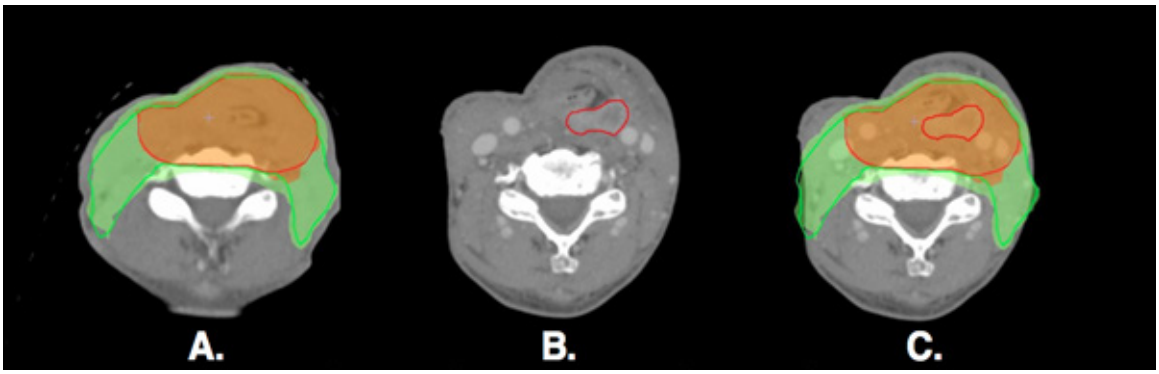

Figure 4. In-field recurrence.

A 60-year old male patient diagnosed of laryngeal squamous cell carcinoma cT4N1M0 underwent total laryngectomy with modified radical neck dissection. The pathological result was pT4N1M0 with close margin and LVI at tumor bed. After adjuvant radiation 60/54 Gy in 30 Fx, patient developed local recurrence at primary tumor bed within the area of 60 Gy dose.

A. CT simulation with radiation treatment planning dosimetry as following; red color fill indicates dose coverage of PTV HR 60 Gy, green color fill indicates dose coverage of PTV LR 54 Gy.

B. Follow-up CT imaging detected tumor recurrence. Red line indicates gross recurrent lesion (fGTV) at tumor bed.

C. Co-registration of CT simulation and follow-up CT indicates in-field tumor recurrence.

Adverse events

Adverse events are listed in **Table 5.** During and after treatment, most patients had no or minor grade 1 adverse reaction. Grade 3 toxicities of acute reactions were 12%,2% and 12% for mucositis, dermatitis and febrile neutropenia, respectively. The percentage of grade 3 late toxicities were 2% and 6% for dysphagia and skin fibrosis, respectively. None of the patients experienced grade 4 or worse side effects. There was no skin toxicities associated with flap reconstruction complications.

Discussion

Our institute started radiation treatment with one linear accelerator in 2015. This is the first retrospective report of radiation treatment in head and neck cancers in Thammasat hospital, limited number of patients as it may, our result was comparable to previously published studies[12,14]. IMRT has been implemented initially for head and neck cancers in Thailand since early 2000s[15]. Highly conformal radiation techniques using Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc

Table 5. Adverse events according to the National Cancer Institute Common Terminology Criteria of Adverse Events CTCAE version 4.0.

Toxicities	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute					
Mucositis	9	13	6	0	-
Dermatitis	34	11	1	0	0
FNP	-	-	6	0	0
Weight loss	10	7	0	-	-
Late					
Xerostomia	28	5	0	-	-
Dysphagia	1	0	1	0	0
Fibrosis	32	4	3	0	0

Abbreviations.FNP febrile neutropenia.

Therapy (VMAT) has now become the standard radiation treatment with available consensus contouring guideline[16]. Clinical judgement played prominent role in determining if IMRT or VMAT is appropriate in each case as there is no significant difference in PTV coverage and biological parameters are comparable[17]. Multiple clinical evidences[18,19,20] reported that IMRT improved overall survival and locoregional control while decrease radiation toxicities and it was well tolerable even in elderly patients[21]. Standard guidelines[22,23] are available to standardize treatment of head and neck cancers among each institute. Radiotherapy in this study was well tolerated without any surgical wound or flap related complications. The shortest RT treatment of 14 days resulted from toxicities of grade three mucositis and grade one weight loss. Patient then deliberately discontinued further radiation, however there was no disease failure detected upon recent clinical follow-up in this case. The prolonged radiation course of 71 days was due to grade three febrile neutropenia toxicity which led to physician's decision of radiation interruption. The treatment was then continued to completion and no disease failure was found upon follow-up.

Most of the patients were locally advanced stage IVA according to AJCC 7th. Further categorization of available pathological data using AJCC 8th edition also confirmed the result. Oral cavity was the most common subsite of head and neck cancers in this study. The demographic data was correlated with the overall national cancer incidence in Thailand where oral cavity was also the most common subsite of head and neck

primary cancers[24]. The fact that available evidences[25,26] reported this subsite to have worst prognosis in overall head and neck cancers might explains the inferior overall survival rate in our study. The reported 2-year OS 85% by Yao et al reflected oropharyngeal primary being the majority in that study[26]. The study included both definitive and postoperative radiation with prescribed dose sequentially up to 74 Gy in the first group.

The other consideration is majority of cases were older patients. Up to 29% of patients were older than 70 years and older age was found to be one of poor prognosis factor despite of concurrent chemotherapy. The benefit of chemotherapy decreases in advanced age population as non-cancer death event becomes the competing factor[27]. Development of better geriatric assessment to differentiate between chronological and biological age in order to make better clinical decision is still needed.

Interval time between surgery and the start of adjuvant radiation therapy is also an important issue in adjuvant setting. National Comprehensive Cancer Network[28] recommended the interval time not to exceed six weeks as evidence suggested that prolonged waiting period correlated with poor local control. However, further analysis failed to validate those recommendation as the report[29] founded that not the prolonged delay itself but together with suboptimal radiation dose contributed to worse locoregional control. Analysis from larger national cancer database[30] confirmed that 42 days or less interval time was associated with improved overall survival compared with 50 days or more subgroup. However, there was no significant difference between 42 days or less and 43 to 49 days subgroup in terms of mortality. Median time interval between surgery and the start of radiotherapy of 43 days in our study seems adequate.

Univariate analysis identified that pathological nodal disease N2-N3 and lower neck lymph node involvement in primary oral cavity disease favorably correlated with overall survival.

Locoregional recurrence contributed the most to overall disease failure, similar to previous data [31,32]. Radiologic evaluation found that the most common pattern of locoregional failure was in-field recurrence in which detailed assessment specifically identified that most of in-field recurrence were within high dose region.

Standard treatment of locoregional advanced head and neck cancers had been much improved with novel radiotherapy technique, however locoregional failure remains a challenge to overcome. Since 2000, there has been ongoing effort to correlate radiation target volume contouring with clinical outcome to improve disease control[33,34,35,36]. Higher radiation dose prescription using external beam radiotherapy combined with brachytherapy boost had promising locoregional control[37]. In recurrent setting when role of re-external beam radiotherapy is limited, brachytherapy had also been reported to be an effective approach in salvage therapy[38,39]. Radiation dose intensification by brachytherapy approach has been a proposed

solution to improve locoregional failure and recent updated recommendation with 3D-image planning was available[40]. Distinct physical and biological characteristic of particle allows higher dose to target while minimize dose to adjacent normal tissues[41]. In reirradiation setting, proton radiation treatment aiming to cover gross tumor volume with minimal margin has shown to improve local control with comparable toxicities as the data showed that most recurrence, even after reirradiation, occurred within radiation field. Larger prospective trials are needed as most current data are extrapolated from retrospective report with limited follow up time[42,43].

Another important factor is periparotid nodal recurrence which has been controversial in head and neck cancer treated by parotid-sparing IMRT. Ipsilateral cervical lymph node involvement was reported to be a risk factor of regional parotid nodal failure so the decision of parotid-sparing IMRT should be reconsidered case by case[44,45]. Three out of eight locoregional failure in our study had recurrent lesion at periparotid nodal region after treated with bilateral parotid-sparing IMRT. **Figure 3** is follow-up CT images that detected disease failure at periparotid region. Intensive pretreatment staging using positron emission tomography and high index of suspicion can be a beneficial approach to determine if a patient should be omitted parotid-sparing radiation or not[46].

Concurrent systemic chemotherapy plays an important role in postoperative treatment in patients with high risk features. The fact that this study opted for weekly cisplatin instead of high dose cisplatin every three week despite proven superiority from multiple clinical studies in either definitive and adjuvant setting[47,48,49] may also contribute to inferior treatment outcomes.

In our study, one of two cases that developed out-field locoregional metastasis had received postoperative radiation alone despite the presence of lymph node extracapsular extension. The clinical decision was based on patient's advanced age and suboptimal performance status. However, to further improve treatment result in this population which is increasing in aging society, a substitute option should be considered. Established data confirmed that combine radiotherapy with targeted drug such as Cetuximab is well tolerated and it appears better than radiation alone in terms of improved overall survival and local control[50]

Further studies regarding tumor biology correlated with radiation dose or novel systemic therapy might be a solution to improve locoregional failure in this head and neck cancers.

Conclusion

In conclusion, the study found that in-field locoregional failure is the predominant pattern in postoperative radiotherapy in head and neck cancers.

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