Original research

INTENSITY-MODULATED RADIATION THERAPY WITH CONCURRENT CHEMOTHERAPY FOR HEAD AND NECK SQUAMOUS CELL CARCINOMAS: TOXICITY ASSESSMENT

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ABSTRACT

Background: *Intensity-modulated radiotherapy with concurrent chemotherapy attempt to maintain efficiency while limiting toxicity in the treatment of neck squamous cell carcinomas. Side effects of the therapy are both challenge during treatment such as treatment delay, increasing financial and hospitalization rate and also cause early and late toxicities, affects to patient performances and treatment outcomes. We aimed to assess acute and late toxicity in patients with head and neck squamous cell carcinoma (HNSCC) managed with concurrent chemoradiation therapy using intensity modulated radiation therapy (IMRT) technique.*

Methods: *A prospective descriptive study of 120 patients suffering from non-metastatic HNSCC received Intensity-modulated radiotherapy concurrently with four to six cycles of cisplatin (30mg/m2/day/ weekly)from May 2017 to 2018 at Hue Central Hospital (Vietnam). The dose to the primary tumour and cervical lymph nodes totally taken was 70 Gy. Toxicities were gradedbased on the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG).*

Results: *Acute toxicities were mainly at grade 1 with oral mucositis, dermatitis and nausea/vomiting. For late toxicities, grade 3 xerostomia accountings for 5.8%. Neck fibrosis and trismus were not at grade 3 to grade 4, grade 1 mandibular bone necrosis (3.4%) was found in 3 patients.*

Conclusions: *Concurrent chemoradiation therapy with IMRT demonstrated a well-tolerated regime with manageable toxicities.*

Keywords: *Intensity-modulated radiation, Chemotherapy, Toxicity.*

I. INTRODUCTION

Head and neck carcinomas arising from epithelium surface of head and neck region and commonly has squamous cell origin [1]. These subtypes include tumors of parasinuses, oral cavity, nasopharynx, oropharynx, hypopharynx and larynx [2]. In last decades, there have been many prominent advances in head and neck cancer treatment, especially is concurrent chemoradiotherapy indication for locally advanced squamous cell carcinomas, this modality

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could improve tumor control or normal structure preservation [3]. Advances in cancer radiotherapy has affected significantly to outcomes of head and neck cancer treatment thanks to planning optimization, maximum dose increasing, uniform distribution at target volume while minimizing dose to adjacent critical structures. The development of radiotherapy system and inversed planning method (in order to deliver inhomogenous radiation dose) has started a new era of Intensity Modulated Radiation Therapy (IMRT), applied widely in head and neck cancer treatment [4].

Side effects of radiotherapy are both challenge during treatment such as treatment delay, increasing financial and hospitalization and also cause early and late toxicities, affects to patient performance and treatment outcomes [5]. Depending on radiotherapy modalities, total dose can reach up to 70 Gy. Early toxicities such as swallowing, soreness, hair loss, tooth decay and late toxicities such as altered taste sensation, compromised oral hygiene, xerostomia, poor dental condition, poor sleep quality, nutritional deficiency and impaired speech function [6].

Purpose of this study is to analyze certain early and late toxicities in squamous cell carcinomas of head and neck by concurrent chemoradiation therapy with intensity modulated radiation therapy technique.

II. MATERIAL AND METHODS

2.1. Design and patients

We carried a prospective chart review of 120 patients receiving curative concurrent chemoradiotherapy for locally advanced head and neck cancer between May 2017 and May 2018 at Oncology Center, Hue Central Hospital, Vietnam. Eligibility included biopsy provingstage II - IV squamous cell carcinoma of the head and neck according to American Joint Commision on Cancer, for which curative surgical resection was not achievable or by recommendation of multidisciplinary team. Subsites were Oral cavity, Oropharynx, Hypopharynx, Larynx, Nasopharynx, unknown primary was excluded. Youngest patient was 19 years old, and oldest was 85 years old with Kanoffsky performance score were 70% and above. All patients were examined and treated dental conditions before chemoradiotherapy.

2.2. Radiation treatment planning

Radiotherapy technique was IMRT. Patients at first received Computed tomography (CT)simulation with thermomask for head and neck immobilization in supine position. Images from CT simulation and prior CT scans, MRI, PET scans were imported into planning software using Monaco 5.0. Volumes were contoured by radio-oncologists, margins of 0.5 - 1.5 cm were added to gross tumor volumes (GTVs) for subclinical spreading regions (CTVs), and 0.5 cm was added to form PTVs in accounting to daily setup errors. IMRT plans were performed by medical physicists, using Monaco 5.0 version software.

2.3. Radiation dose and delivery

Total dose ranged from 66 Gy to 70 Gy into 30-33 fractions. Fractionation schemes were 2.12 Gy per fraction to Gross tumor (nodes), 1.8 Gy or 1.63 Gy per fraction to high risk volumes and 1.636 Gy or 1.51 Gy fraction to low risk volumes. Each patient was treated by 6 MV photons with dynamic multileaf collimators (dMLC) or Volume modulated arch radiotherary (VMAT). Treatment was provided once a day for 5 sequential days weekly.

2.4. Dose volume analysis of treatment plans

Dose-volume histograms of every treatment plan were assessed before radiotherapy and had to fit several special constraints. Dose to ≥ 95% of the target volume was not to be or less than 5% of the dose prescribed. Dose to ≥ 95% of the prophylactically treated lymph node volume was within +8% to -5% of the dose prescribed. The largest dose to the brain and the spinal cord needed to be <45 Gy and the dose to 50% for every parotid gland needed to be <20Gy.

2.5. Chemotherapy

Concurrent chemotherapy included ciplatin (30mg/m2) weekly given in 4-6 weeks of external beam radiation therapy. Chemotherapy resulted in an absolute neutrophil count <1.000, platele count <100.000, grade 3 dermatitis, and grade 4 mucositis. Radiotherapy was performed 2 hours after cisplastin infusion.

2.6. Assessment of complications

Toxicities were graded based on the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG).Acute radiation toxicities were monitored throughout treatment period by the radiation oncologist weekly. Late toxicities were monitored at planned follow-up visits.

2.7. Follow up

In the first year, every 6 to 8 weeks, patients had a follow-up examination with fiberoptic endoscopy. The examination was arranged every 3 months in the second year and every 4 to 6 months thereafter until the 5th year. . Post-chemoradiotherapy CT was done at 6 to 12 weeks and at 1 year after chemoradiotherapy, though routine CT was performed also periodically up to 2 years after chemoradiotherapy or if clincally indicated. Any suspicious clinical radiographics lesion(s) needed biosy verification prior to treatment failure determination

2.8. Statical analysis

Data was collected and analyzed by SPSS 20.0 software for Windows..

III. RESULTS

A total 120 patients who received definitive concurrent chemoradiotherapy for locally advanced head and neck cancer were prospectively analyzed. Table 1 shows the baseline characteristics of the patients. Most patients were males than women, this might because of Vietnamese males' habits such as alcohol and cigarette consumption. Stage III and IV were 85.8%, many patients came at late stage and experienced other traditional treatments such as traditional medicine, herbals, spiritual yoga for a long time. Dermatitis, oral mucositis, xerostomia and weight loss were common early toxicities, seen in most patients **(Table 2)**. Xerostomia and neck fibrosis were most common late toxicities of HNC patients, though were in low grade, only 7 cases had grade III xerostomia **(Table 3)**.

Table 1: Patients' characteristics

Patients' characteristics	n	%
Age	55.88 ±1.20	
Gender	[19- 85]	
Male	102	85
Female	18	15
Tumor location		
Oral cavity	26	21.7
Oropharynx	22	18.3
Hypopharynx	25	20.8
Larynx	14	11.7
Nasopharynx	33	27.5
Staging		
Tumor (T)		
T1-2	38	31.6
T3-4	82	68.4
Node (N)		
N0-1	78	65.0
N2-3	42	35.0
Clinical staging		
II	17	14.2
III	62	51.6
IV	41	34.2
Differentiation grade (n= 87)		
I	28	32.2
II	28	32.2
III	25	28.7
IV	6	6.9
Nasopharynx pathology		
(n= 33)	2	6.1
Type 1-WHO	4	12.1
Type 2-WHO	27	81.8
Type 3-WHO		

Table 2: Early toxicities

Toxicity (N=120)		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	n	0	58	58	4	0
	%	0	48.3	48.3	3.3	0
Oral mucositis	n	0	18	94	8	0
	%	0	15.0	78.4	6.6	0
Xerostomia	n	0	58	62	0	0
	%	0	48.3	51.7	0	0
Nausea/vomitting	n	95	14	11	0	0
	%	79,1	11.6	9.2	0	0
Weight loss	n	0	51	69	0	0
	%	0	42.5	57.5	0	0

Table 3: Late toxicities

Toxicity (N=120)	Grade (%)				
	0	1	2	3	4
Xerostomia	0	91 (75.8)	22 (18.3)	7 (5.8)	0
Neck fibrosis	0	95 (79.1)	25 (20.9)	0	0
Trismus	77 (64.2)	38 (31.6)	5 (4.2)	0	0
Mandible necrosis	116 (96.6)	4 (3.4)	0	0	0

IV. DISCUSSION

Mean age of patients was 55.88 ± 1.20 (from 19 to 85 y.o), male was 85%. In our study, all hypopharynx and larynx patients were males. This might because males related to morecancer risks: cigarette and alcohol consumption.

Primary tumor location: rates of oral cavity, oropharynx, hypopharynx, larynx and nasopharynx cancer were 21.7%, 18.3%, 20.8%, 11.7% and 27.5% respectively.

Clinical stage: 68.4% patients was T3-4, 35% was N2-3. Percentage of stage III, IV were 51.6% and 34.2%, respectively. Cell diferrentiation of head and neck carcinomas (nasopharynx was excluded) was quite similar at grade I, II and III. Undiferrentiated carcinoma was 6.9%. Type III - WHO was 81.8% for nasopharynx carcinoma.

Acute toxicities are commonly at skin, oral mucosa and saliva glands. The larger radiotherapy field is, the more severe lesions of skin, oral mucosa and saliva glands are, especially to head and neck cancer because of large radiotherapy field, covering primary tumor and lymph nodes. Common clinical symtomps are swelling skin, oral ulcer and xerostomia. Many studies confirmed oral ulcers is the first and most common complication in head and neck cancer radiotherapy, accounting to 80-90% of patients and presented early during radiotherapy process and prolonged about 2-3 weeks post-treatment. By routinely radiotherapy techniques, it was likely to protect main saliva glands such as parotid and submandibular glands from radiation beams. Lesions at these glands cause many grades of xerostomia.

In this study, most complications of dermatitis, oral muscositis, xerostomia were grade I and II, grade III were low rate (dermatitis 3.3%, oral mucositis 6.6%), there was no grade IV complication, similar

to studies of Ozedemir et al [7] and Songthong et al [8]. Van et al studied IMRT on 78 patients showed grade III, IV dermatitis was 6% [9].

For oral mucositis, patients with grade III oral mucositis were delayed radiotherapy, received intensive medical treatment by anti-mucosa burn medications (contains Nepidermin), they recovered 3-5 days into grade II and were able to continue radiotherapy. Garden et al, grade III and IV oral mucositis were 74% and 2% respectively [10]. In study of Ozedemir et al., 45 nasopharynx cancer patients treated by concurrent chemoradiotherapy with IMRT technique, grade I, II and III oral mucositis were 37.7%, 55.6% and 6.7% respectively, there was no grade IV [7]. Songthong et al studied 73 stage II-IVB nasopharynx patients from 2005-2011, treated by concurrent chemoradiotherapy (IMRT technique): grade III oral mucosistis was 16.4% [8].

In our study, 95.4% of patients was oral mucositis, mostly at first week of radiotherapy process, presented by hot-burnt sensation, at second week, they felt painful when chewing and swalowing, examinations showed prominent edema, incresed saliva. There was only one patient had grade III oral mucositis, no grade IV. Acording to many studies, IMRT did not decrease toxicity on skin and mucosa in general, however, because of focusing capacity on tumor and decreasing doses to normal adjacent structures, combining to precise treatment of Image guided radiotherapy help prevent grade IV skin and mucosa toxicities. Meta-analysis comparation IMRT to conventional radiotherapy showed quality of life of head and neck cancer patient treated by IMRT was better than conventional radiotheray. This is prominence of IMRT.

For nausea, our study showed grade I and II was 20.8. Xerostomia, oral mucositis, fatigue, anorexia combine to nausea makes nutritional status decrease, lead to weight loss. Percentage of grade I, II weight loss in our study was 42.5% and 57.5% respectively. Songthong et al when treated 73 nasopharynx cancer patients by concurrent chemoradiotherapy with IMRT technique showed grade III weight loss was 28.6% and most of patient weight was recovered at 2 years post-treatment [8].

Generally, acute toxicities on skin, mucosa, GI tracts and weight in concurrent chemoradiotherapy with IMRT technique were much lower than 3DRT technique.

Late toxicities had been evaluated from day of 90 post treatment, according to radiotherapy induced late complication classification system of RTOG/EORTC. In head and neck cancer radiotherapy, late toxicities include xerostomia, skin fibrosis, trismus and mandibular necrosis.

In our study, xerostomia was mostly at grade I (75%) and II (18.3%), grade III was low (5.8%). Study of Nancy Lee et al., evaluated xerostomia in 68 nasopharynx cancer patients treated by concurrent chemoradiotherapy with IMRT technique at 1 year post treatment, showed grade I and II xerostomia were 51.9% and 13.5% respectively; no grade III and IV [11]; Wang et al., evaluated late toxicities in 138 nasopharynx cancer patients treated by concurrent chemoradiotherapy with IMRT technique, showed grade III xerostomia was 11.63% [12]. Pan et al showed grade I and II xerostomia were 71.83% and 18.31% respectively, no grade III and IV [13]. Zeng Y et el., studied on 208 nasopharynx cancer patients treated by concurrent chemoradiotherapy with IMRT technique, considered no grade III and IV xerostomia and xerostomia improved by time after 1,2,3,4 and 5 years were 80.8%, 66.3%, 56.0%, 40.9%, 40.9% [14]. According to Marta et al., showed though there was no difference in local-regional control and overall survival, but IMRT for head and neck cancer had proved to decrease xerostomia grade II to IV comparing to 3DRT; a special notice was 82% patients in study was nasopharynx cancers [15].

De Felice et al. (2017) evaluated 30 IMRT plans for tonsil and larynx cancer, these plans aimed to

prevent radiation dose to parotid and submandibular glands while maintained aims to target volumes. In conclusions, to larynx cancer, with a similar radiation prescriptive dose, dose decreased 23% to parotid glands and 7% to submandibular glands. To tonsil cancers, these rates decreased to 31% and 7% respectively [16].

Skin fibrosis in neck radiation field was common presented, mostly was at grade I and II, if patient was at grade III and IV, there should be affects to neck movement. In our study, neck skin fibrosis was mostly at grade I (79.1%) and II (20.9%), no grade III and IV. Chen et al showed neck fibrosis grade I was 77.46%, grade II was 14.08% no grade III and IV [17].

During radiotherapy process, radiation field includes temporal mandibular joint, masticator muscles, makes patient difficult to open mouth, affects to food intake. At 6 month post treatment evaluation, we recorded that grade I trismus was 31.6%, grade II was 4.2%, no grade III and IV. 62% of patients did not have trismus. According to Pan Xin-Bin et al., grade I and II trismus were 84.51% and 4.23% respectively, no grade III and IV [13].

Our study reported 4 cases with mandibular necrosis, was 3.4%. According many authors, post treatment mandibular necrosis was very rare, and at very low rate if presented [14].

V. CONCLUSION

Concurrent chemoradiotherapy for squamous cell head and neck cancer with IMRT technique showed early and late toxicities in very low rate, mostly at grade I and II. Patients tolerated modality easily, assure maintaining quality of life during and after treatment.

CONFLICT OF INTEREST

There are no conflicts of interest.

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