



## RADIATION THERAPY OF HEAD AND NECK SQUAMOUS CELL CARCINOMA IN LOW-INCOME COUNTRIES

Karamyan N.

Department of Radiotherapy, National Centre of Oncology, Yerevan, Armenia

### Abstract

The paper presents challenges of radiation therapy of head and neck squamous cell carcinoma in the countries with low income, where the technical possibilities are limited. Some preliminary results of ongoing own clinical trial, investigated the ways of improvement for radiotherapy results in low-income countries, are presented. The collected data based on the results of treatment of 397 HNSCC patients shows the considerable improvement of therapeutic gain, reached by the use of altered regimens of fractionation, concomitant radio-chemotherapy and preventive treatment of expected acute and late toxicities. Some preliminary conclusions are suggested for further discussion.

*Keywords:* head and neck cancer, radiation therapy, low-income country, altered fractionation, radiation toxicities

### Introduction

The incidence of cancer in the world is increasing, particularly in relation to prolonged life expectancy from worldwide improvements in standards of living. According to recent estimates of the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), approximately ten million new cancer cases are being detected per year worldwide, with slightly more than half of the cases occurring in developing countries. By the year 2015 this number is expected to increase to about 15 million cases, of which two thirds will occur in developing countries. At the same time, due to successes of modern medicine, about half of these patients can be cured radically [IAEA, 2007].

The Squamous Cell Carcinoma of the Head and Neck (HNSCC), according to various authors, accounts for 5 - 6 % from the general number of all malignant diseases. Annually, in Europe 95000 new HNSCC patients are registered, and mortality makes 43000 cases a year, and worldwide - 644000 and 352000, respectively [GloboCan 2002,].

The incidence of HNSCC and rates of its growth in the world for the last two decades were relatively stabilized; however, their accurate distinction between the developed and developing countries, where disease continues to grow, was revealed.

### Address for Correspondence:

Radiotherapy Department, National Center of Oncology,  
76 Fanarjyan str, Yerevan, Armenia.  
Tel.: (+37410) 287 220, (+37493) 228 945  
Fax: (+37410) 287 051  
E-mail: ners\_karamyan@yahoo.com

According to IARC data for 2002, from the most widespread localisations of HNSCC, the larynx cancer in structure of the general malignant diseases in the world has occupied the 18<sup>th</sup> place in the developed countries and 16<sup>th</sup> in the developing countries (68 thousand vs. 103 thousand), and among men a larynx cancer has occupied the 13<sup>th</sup> and 11<sup>th</sup> place, respectively (60 thousand/89 thousand), while cancer of pharynx – the 14<sup>th</sup> and 12<sup>th</sup> places, respectively (43 thousand/71 thousand) [IAEA, 2007].

The prominent feature of HNSCC is that the majority of patients are already at the locally-advanced, but not metastatic stage of the disease (about 60% of patients) at the moment of a diagnosis. Due to this fact, at HNSCC treatment the methods of local influence have major importance: surgery and radiotherapy (RT) [Sanderson R. , Ironside J. , 2002].

Numerous randomized studies have shown that chemotherapy, as a method of primary treatment for HNSCC does not improve the rates of overall and disease-free survival in comparison with local treatment; it is used now in a combination with surgery or radiotherapy, as an induction component or concurrently [Pignon J. et al., 2000; 2005; 2007].

The RT alone has long been the standard non-surgical treatment of locally advanced HNSCC. This can be explained by the fact that the majority of head and neck tumours are rather radiosensitive, and there are no any substantial contra-indications for the radiation therapy of this contingent

of patients, practically. Besides, not conceding surgery in efficiency, RT provides better functional and cosmetic effect [Halperin E. , et al., 2008].

In HNSCC treatment, RT is used in curative, adjuvant, and palliative purposes. Now RT is applied for in 70-85% of HNSCC patients; in 50-70 % of them it is used as a treatment principal mode.

Thanks to the achievements reached for last decades in the field of radiation and computer technologies, radiobiology, pharmacology, etc., it was possible to considerably raise the efficiency of RT, both in concern of the local control and in concern of the overall and disease-free survival rates. The transition from conventional technologies to more modern ones, from cobalt sources to linear accelerators, occurrence of three-dimensional computer planning, conformal irradiation, IMRT, and then IGRT and adapted RT allowed to improve results of treatment considerably [Bourhis J. et al., 2005; Ding M. et al., 2005; Harari P. , 2005; Van Dyk J., 2009; Vikram B., 2009].

Besides, the application of altered regimens of fractionation also leads to improvement of the locoregional control by 7-10 %, and application of concurrent chemotherapy - by 8 % [Jeremic B. et al., 2000; Bernier J. et al., 2001; Adelstein D. et al., 2002; Antognoni P. et al., 2005; Halperin E. et al., 2008].

On the other hand, application of more modern technologies allows not only to increase the dose to the target volume, but also to reduce the irradiation of surrounding healthy tissues and organs at risk that leads to the reduction of frequency of acute and late toxicities of RT, thus ensuring improvement of quality of life of patients.

Unfortunately, introduction of the specified methods of treatment in routine clinical practice demands considerable financial investments on equipment acquisition, maintenance service, training of staff, additional payment to the personnel

at non-conventional regimens of fractionation. Currently, the majority of low-income countries have no possibility of wide application in practice of linear accelerators, conformal irradiation, IMRT and other more modern technologies.

The given circumstance, undoubtedly, is reflected in results of treatment and toxicity of RT in the countries where the public health services are insufficiently financed. Therefore, there is a necessity for search of alternative ways to increase the efficiency of RT

Nowadays, the only existing Department of Radiation Oncology in Yerevan treats approximately 1500 - 1600 patients in a year. The Department is supplied by one linear accelerator, 3 cobalt devices (2 of which were made more than 25 years ago in the USSR), simulator, CT-scan, three-dimensional planning system, necessary dosimetric equipment. The compelled application of rectangular fields of irradiation, constant failure of the linear accelerator, absence of multileaf collimator, IMRT and so on, considerably limits the technical possibility of irradiation of HNSCC patients because of impossibility to apply higher doses on a target and impossibility of restriction of the irradiation of organs at risk. The given circumstance is reflected substantially in rates of the local control and incidence of late RT reactions.

Since 2008 a clinical trial investigating the ways to increase HNSCC radiotherapy efficiency has been initiated by us. Patients with HNSCC treated by RT during the period from 2004 to 2008 were involved by the trial.

#### **Materials and Methods**

In total 611 HNSCC patients were included in the research. Ninety six of them (15.7%) had cancer of oral cavity and tongue, 59 (9.6%) - cancer of oropharynx, 133 (21.8%) - cancer of a nasopharynx, nasal cavity and paranasal sinuses, 323 (52.9%) - cancer of larynx and hypopharynx (Table).

Table.

Distribution of patients by tumour sites and years

Tumour sites	2004	2005	2006	2007	2008	Total
Oral cavity/tongue	22	18	16	17	23	96 (15.7%)
Oropharynx	13	10	12	11	13	59 (9.6%)
Nasopharynx	31	21	23	31	27	133 (21.8%)
Larynx/hypopharynx	50	51	73	76	73	323 (52.9%)

The RT with curative intent has been applied to 397 patients; the remaining 214 patients received RT as an adjuvant or palliative treatment. Among 397 patients 255 (64.2 %) were in locally-advanced stages of disease (III – IV stages).

The patients receiving RT with curative intent were divided in two groups by the fractionation mode. 135 (34 %) from them were treated by standard conventional fractionation: 1.8–2.0 Gy/5 fr per week to the total dose 60 - 66 Gy. For the purpose to increase RT efficiency, in other group of patients (262 pts; 66 %) the alternative regimen of fractionation – moderately accelerated fractionation with dose escalation per fraction – 1.8 – 2.5 Gy /5-6 fr per week to the total dose equivalent to 66 Gy was applied. As a result, the overall treatment time was shortened on the average by 5-6 days in comparison with the conventional treatment.

The concurrent radio-chemotherapy has been applied to 76 patients (29.8 %) with HNSCC at III - IV stages of disease. For the purpose to reduce the treatment overall toxicity we, basically, applied monochemotherapy by weekly cisplatin 50 mg within the last 3 weeks of the irradiation. The given circumstance has allowed us to deliver the treatment in the planned volume to all 76 patients and without breaks in the treatment.

Since 2004, for prevention and treatment of acute skin and mucosal toxicity we have applied a complex of prophylactics based on various medicinal plants and consisted from oil extracts, infusions, and inhalations. Currently this complex is modified and by us in the routine clinical practice of HNSCC treatment, obtaining the Patent on Invention is expected.

### Results

This paper presents only preliminary results of our research. The data on the overall and disease-free survival will be reported after summarizing the trial outcomes.

From 397 HNSCC patients, which received RT with curative intent, the complete tumour response (CR) was achieved in 66 pts. (16.6%), partial response (PR) - in 227 pts. (57.2%). Among the patients receiving RT with a conventional fractionation, the CR has been seen in 16 pts. (11.8%), the PR - in 71 pts. (52.6%). The overall rate of loco-regional response has made 69 %. In the patients receiving RT in accelerated mode of

fractionation with escalation of dose, the CR was revealed in 50 pts. (19.1%), the PR - in 156 pts. (59.5%). The overall rate of loco-regional response made 81.4 %.

In the patients receiving concurrent radio-chemotherapy, the results of loco-regional control were higher: CR - 24,6 %, PR - 74 %. The overall rate of loco-regional response was 89.9 % (Figure).

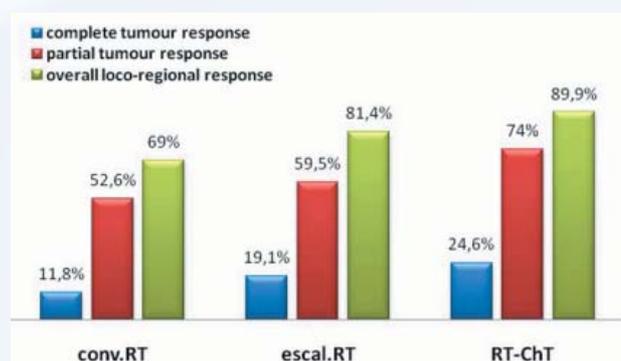


Figure. The rates of tumour response depending on the irradiation mode

Acute radiation reactions of grade II - III were observed almost in all patients receiving escalated RT and concomitant radio-chemotherapy (97.3 % of patients). However, due to applied complex of prevention and treatment of acute radiation reactions developed by the authors, the toxicity remained at a tolerable level and treatment was delivered in the planned volume to all patients without the compelled interruptions of treatment.

### Preliminary conclusions

The locally-advanced HNSCC can be treated successfully by means of conventional technologies in developing countries with the low-income.

The application of altered regimens of fractionation and concomitant chemotherapy allows to improve the results of the radiotherapy delivered by Cobalt 60 units. There is a need for developing of more sophisticated methods of irradiation (3D-conformal RT) for Co 60 based equipment, which is more cost-effective comparing with linear accelerators.

The use of the various means based on medicinal plants and some anti-inflammatory preparations allows to implement more aggressive radiation therapy at tolerable level of radiation toxicity.

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Squamous cell carcinoma of the head and neck derive from different sites, including oral cavity, oropharynx, nasopharynx, hypopharynx and larynx. In oropharyngeal squamous cell carcinoma, in some extent depending on the country or continent, p16 marks HPV high-risk positive cases up to 100 %, but down to 80 % [12, 13], due to the prevalence of infections by subtype HPV type 16. Other types, including type 18 does not seem to be related to stable p16 expression. Histologically, a squamous cell carcinoma can be challenging in case of low differentiation or basaloid differentiation and depending on the surrounding inflammatory infiltration. Cutaneous squamous cell carcinoma (SCC) is a common cancer arising from malignant proliferation of the keratinocytes of the epidermis that has invaded into the dermis. Carcinoma of the lip and selected sites of head and neck skin. A clinical study of 896 patients. *Radiother Oncol* 1987; 8:11. Topical combination therapy for cutaneous squamous cell carcinoma in situ with 5-fluorouracil cream and imiquimod cream in patients who have failed topical monotherapy. *J Am Acad Dermatol* 2006; 55:1092. Goh MS. Invasive squamous cell carcinoma after treatment of carcinoma in situ with 5% imiquimod cream. *Australas J Dermatol* 2006; 47:186. Rowe DE, Carroll RJ, Day CL Jr. Squamous cell carcinoma begins in the tissues that line the air passages in the lungs. It is also known as epidermoid carcinoma. Most squamous cell carcinomas of the lungs are located centrally, usually in the larger bronchi that join the trachea to the lung. Verywell / Julie Bang. Symptoms. Squamous cell carcinoma tends to cause symptoms earlier because it affects the larger airways of the lungs (as opposed to adenocarcinoma which affects the edges). While this translates to higher rates of early detection, 75 percent of cases are still only diagnosed after the cancer has spread. Squamous cell carcinoma is the most common cause of Pancoast syndrome (also known as superior sulcus syndrome).