# Head and neck cancer in young adults treated with 3-D conformal radiotherapy

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## SUMMARY

**Background:** *Purpose of this study was to determine patterns of failure in young adults with head and neck cancer treated with 3-D conformal radiotherapy.*

**Methods:** *Twenty-eight patients with head and neck cancer younger than 41 years of age were treated with 3-D conformal radiotherapy. Patients' median age was 31.4 years. Radiotherapy was delivered in the median total dose of 67.2 Gy to PTV (range, 60.0-70.0 Gy) with or without concurrent cisplatin.*

**Results:** *The median duration of follow-up was 20 months. Distant metastases were the most frequent pattern of failure. The locoregional relapse-free survival (LRR-FS) rate at 2 years was 66.6%. The median duration of LRR-FS was 15 months. The distant metastases relapse-free survival (DMR-FS) rate at 2 years was 65.7%. The median duration of DMR-FS was also 15 months. The overall survival (OS) rate at 2 years was 57.2%. The median duration of OS was 20 months.*

**Conclusion:** *Radiotherapy with or without concurrent chemotherapy plays an important role in treatment of patients with head and neck cancer. Recent developments of new radiotherapy techniques have increased rates of local control. Distant metastases remain the most frequent pattern of failure in this group of young adults with head and neck cancer. Introducing new cytotoxic and target therapies in future could lead to better outcome in this subgroup of patients.*

**Key words:** *Head and Neck Neoplasms; Young Adults; Radiotherapy, Conformal*

**Abbreviations:**
HN – Head and Neck, 3DCRT – three-dimensional conformal radiotherapy; CT – computed tomography; MRI – magnetic resonance imaging; 3-D – three-dimensional; DICOM – Digital Imaging and Communications in Medicine; OR – Organs at Risk; GTV – Gross Tumor Volume; CTV – Clinical Target Volume; PTV – Planning Target Volume; TPS – Treatment Planning System; ICRU – International Commission on Radiation Units and Measurements; DAHANCA – Danish Head and Neck Cancer Group; EORTC – European Organization for Research and Treatment of Cancer; GORTEC – Groupe d'Oncologie Radiothérapie Tête et Cou; NCIC – National Cancer Institute of Canada; RTOG – Radiation Therapy Oncology Group; ECOG – Eastern Cooperative Oncology Group; LR-RFS – locoregional relapse-free survival; DM-RFS – distant metastases relapse-free survival; OS – overall survival; HPV – Human papillomavirus



## INTRODUCTION

Head and neck (HN) cancer is one of the most common cancers in the Southern Europe (1). This cancer type usually occurs after the age of 60 or 70 and is associated with tobacco and alcohol consumption, which are considered to be the major etiological factors, although recent findings are supporting the fact that an increasing number of HNSCC cases are associated with viral infections.

With around 350 new cancer cases annually, head and neck cancer is the 6th most common cancer among male patients and the 9th among female patients in the Republic of Macedonia (1).

The incidence of HN cancer in the world, in young population, is approximately 1% - 8% of all head and neck cancer cases, based on recent findings (2-5). These figures projected on a country level, predict an expecting incidence of up to 32 new cases in young population with HN cancer.

Epidemiological characteristics of HN cancer cases among young population are likely to be different, compared with this cancer in overall population. Considering gender distribution, some studies demonstrated higher relative incidence in female patients than in male patients (5-7) or even a reversal distribution of ratio (8).

Regarding the site, the incidence of HN cancer is more likely to occur in the oral cavity and oropharynx (9) than in other subsites, and in nasopharynx as reported in our study.

The association of oropharyngeal cancer with HPV infection led to conclusion that there is viral etiology in development of this subtype in young population (3, 10), however, connection between the oral cancer and HPV remains controversial (11, 12).

Head and neck cancer in young population is more likely to occur in more advanced stages (which was published in small institutional studies (13, 14)), but again, this issue is controversial, because some of the studies are reporting that younger patients are more likely to be presented with more localized disease than older patients (10).

In the study by Garavello et al., authors suggested that younger age could be an independent prognostic factor of worse survival and that the possibility of treatment of younger patients in a different form from their older counterparts should be considered (15).

Head and neck cancer is radiosensitive disease, so radiotherapy remains compulsory treatment modality, acting alone or in combination with surgery and chemotherapy (16, 17). In this group of patients, radiotherapy remains a corner stone of management of this disease.

## PATIENTS AND METHODS

Between January 2005 and July 2008, 28 patients with head and neck cancer younger than 41 were treated at the University Clinic of Radiotherapy and Oncology in Skopje. On the day of the first consultation, patients histologically verified the head and neck cancer and were staged with available imaging and clinical modalities. All patients underwent panendoscopy, computed tomography of head and neck region (from clavicles to the base of the scull), chest x-ray, ultrasound of abdominal organs and basic lab tests, which included hepatic enzymes, urea, creatinine, and complete blood count. If some of the findings were positive, patients underwent additional examinations for verification of the stage of the disease.

Before the beginning of treatment, all patients signed a written consent form, according to institutional and national rules. This consent form is available upon request and is kept by the editor of this paper.

Radiotherapy was introduced on linear accelerator Varian 23EX (dual photon energy and six energies of electrons) in accordance with a three-dimensional conformal radiotherapy (3DCRT) plan. A thermoplastic head

and shoulders mask was used for patients' immobilization in order to assure the reproducibility of the treatment. Treatment planning CT scans were carried out in the treatment position. Patients were positioned supine and treatment scans were performed with slice thickness of 5 mm, from scull vertex to 2 cm inferior from sternoclavicular joint in order to assure sufficient reconstruction of 3-D patient model.

After CT simulation and marking of initial isocenter, DICOM images were imported in planning system and target volumes and OR volumes were contoured using available tools in TPS (Varian Medical System, Eclipse version 7.3.1).

The definition of contoured volumes and organs of risk was as recommended by ICRU Report 62 (18). Delineation of the neck lymph node levels was according to DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines (19) and proposals for the delineation of the nodal CTV in the node-positive and the post-operative neck (20).

In postoperative radiotherapy, the sites of surgically removed primary tumors and metastatic lymph nodes represented the clinical target volumes CTV60 or CTV66. The clinical target volume CTV50 included CTV60 or CTV66 and all levels of cervical lymph nodes recommended for elective irradiation. In definitive radiotherapy, the gross tumor volume GTV70 was defined as the extension of the primary tumor and the gross nodal disease if present. The clinical target volume CTV50 was defined as GTV70 plus a margin for the potential microscopic extension of the disease. This volume also included those lymph nodes considered for elective irradiation. In definitive radiotherapy of nasopharyngeal carcinoma, the gross tumor volume (GTV70), also known as CTV70, was defined as the extension of the nasopharyngeal tumor and the gross nodal disease revealed by physical examination and by imaging procedures. The high-risk clinical target volume (CTV59.4) was defined as CTV70 plus a margin for the potential microscopic extension of the disease. This volume also included those lymph nodes considered to be of high risk as: submandibular lymph nodes; upper jugular lymph nodes; midjugular lymph nodes; posterior cervical lymph nodes, and retropharyngeal lymph nodes. The low-risk clinical target volume (CTV50.4) referred to the lower jugular lymph nodes and supraclavicular lymph nodes. The planning target volumes were PTV70, PTV66, PTV60, PTV59.4, PTV50.4, and PTV50. They provided a margin of 0.5 cm around the adequate CTV to compensate for the variability of treatment set-up and internal organ motions.

Chemotherapy protocol consisted of cisplatin 30 mg/m$^2$ administrated according to protocol with determined timeframe, given to the patients concomitantly with radiation on a weekly basis, starting on the first day of radiotherapy. A complete blood count and biochemistry were checked weekly before chemotherapy, in order to asses hematological toxicity of treatment and respectively, chemotherapy was administered or was discontinued depending on toxicity.

The first assessment of tumor response was performed three months after completion of definitive radiotherapy with or without concurrent chemotherapy by physical examination, fiber-optic endoscopy and head and neck MRI. The evaluation of response was also assisted by biopsy of any suspicious residual lesion. Complete response was defined as complete disappearance of locoregional disease. Partial response was defined as tumor shrinkage of $\geq$ 50% of the sum of the product of perpendicular diameters of all measurable lesions.

## STATISTICAL ANALYSIS

The end points examined, were locoregional relapse-free survival (LR-RFS), distant metastases relapse-free survival (DM-RFS) and overall survival (OS). LR-RFS and DM-RFS were evaluated and calculated from the first day of treatment until the day of first occurrence of primary, neck, or distant relapse, or until the day of the last follow-up. Patients who did not achieve complete response after treatment had the same starting and terminating point and they were assigned a LR-RFS of 0 months. The starting point for OS was the date of commencement of treatment, and the terminating point was the date of death or the date of the last follow-up. The LR-RFS, DM-RFS and OS curves were constructed using the Kaplan-Meier method (21).

## RESULTS

Detailed patient and tumor characteristics are reported in Table 1. The male to female ratio was 1:1 (Figure 1). Patients' median age was 31.4 years (range 16-40). All patients were with ECOG performance status 0.

**Table 1. Baseline characteristics (total patients = 28)**

| **Patient characteristics** | |
|---|---|
| Gender: | |
| male | 14 (50.0%) |
| female | 14 (50.0%) |
| Median age (years) | 31.4 years (range 16-40 years) |
| ECOG performance status: | |
| 0 | 28 (100.0%) |
| 1 | 0 (0%) |
| **Tumor characteristics** | |
| Site of primary tumor: | |
| oral cavity | 7 (25.0%) |
| oropharynx | 3 (10.7%) |
| hypopharynx | 2 (7.1%) |
| nasopharynx | 9 (32.2%) |
| larynx | 2 (7.1%) |
| salivary gland | 4 (14.3%) |
| paranasal sinuses | 1 (3.6%) |
| Histology: | |
| squamous cell carcinoma | 14 (50.0%) |
| lymphoepithelioma | 7 (25.0%) |
| adenocarcinoma | 5 (17.9%) |
| tumor mixtus malignum | 2 (7.1%) |
| T stage: | |
| T1 | 1 (3.6%) |
| T2 | 7 (25.0%) |
| T3 | 12 (42.8%) |
| T4 | 8 (28.6%) |
| N stage: | |
| N0 | 13 (46.5%) |
| N1 | 2 (7.1%) |
| N2 | 12 (42.8%) |
| N3 | 1 (3.6%) |
| Stage: | |
| I | 0 (0%) |
| II | 4 (14.3%) |
| III | 11 (39.3%) |
| IVA | 11 (39.3%) |
| IVB | 2 (7.1%) |
| **Treatment characteristics** | |
| Type of radiotherapy: | |
| postoperative radiotherapy | 12 (42.8%) |
| definitive radiotherapy | 16 (57.2%) |
| Total dose (Gy) | |
| 60 | 5 (17.9%) |
| 66 | 7 (25.0%) |
| 70 | 16 (57.2%) |

Nasopharynx and oral cavity were the most frequent sites of the primary tumors. Squamous cell carcinoma was present in one half of patients while lymphoepithelioma was present in one quarter of patients (Figure 2). Stage III and stage IVA were equally presented.

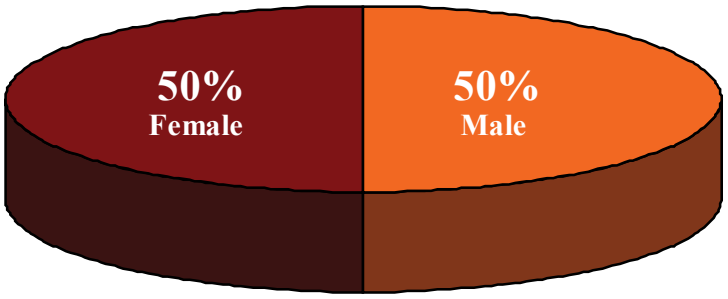


**Figure 1. Distribution of patients according to sex**

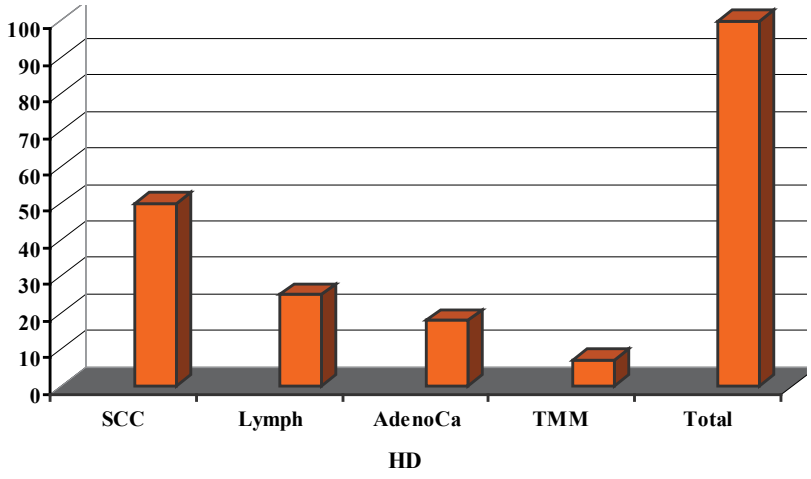


**Figure 2. Distribution of patients according to histological diagnosis**
SCC: squamous cell carcinoma, Lymph: lymphoepithelioma, AdenoCa: adenocarcinoma, TMM: tumour mixtus malignum, HD: histological diagnosis

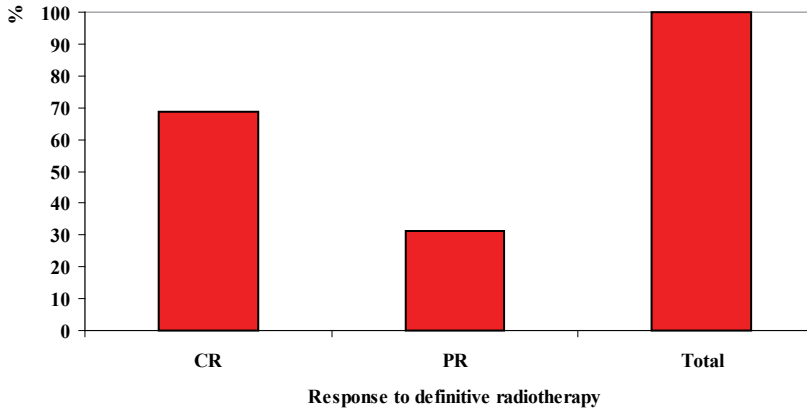


**Figure 3. Distribution of patients according to response to treatment**
CR: complete response, PR: partial response

Postoperative radiotherapy was realized in 12 patients (42.8%). Definitive radiotherapy with or without concurrent chemotherapy was delivered in 16 patients (57.2%). The median total dose was 67.2 Gy (range, 60.0-70.0 Gy). In the group treated with definitive radiotherapy, 13 patients (81.3%) received concurrent chemotherapy. Only 2 patients completed all 7 cycles, and 61.5% had 6 cycles of concurrent chemotherapy. The mean total dose of cisplatin given was 298 mg/m2 ± 63.9 SD.

Three months after completion of treatment in the group treated with definitive radiotherapy with or without concurrent chemotherapy, 11 patients (68.8%), and five patients (31.2%) had a complete response and partial response, respectively, giving an overall response rate of 100% at the primary site (Figure 3).

The median duration of follow-up was 20 months (range: 7-50). Patterns of failure in patients treated with postoperative radiotherapy and in patients who had experienced complete response following definitive radiotherapy are given in Table 2.

**Table 2. Tumor recurrence and metastases in patients treated with postoperative radiotherapy and in patients treated with definitive radiotherapy who achieved complete primary and nodal response**

| Pattern of failure | No. of patients | % |
|---|---|---|
| Local recurrence | 2/23 | 8.7 |
| Regional recurrence | 1/23 | 4.3 |
| Locoregional recurrence | 1/23 | 4.3 |
| Distant metastases | 6/23 | 26.1 |
| Local recurrence and distant metastases | 1/23 | 4.3 |
| Total | 11/23 | 47.8 |

Treatment failure was noted in 11 patients (47.8%). Distant metastases were the most frequent event of failure present in 6 patients (54.5%) (Figure 4). Local recurrence was diagnosed in 2 patients (18.2%) (Figure 4). Distant metastases and local recurrence was present in only one patient (9.0%) (Figure 4). Four patients remained alive at the closeout date. Five patients died after developing distant metastases, three patients died because of local or locoregional relapse, and five patients with partial response following treatment died because of the progression of the persistent disease.

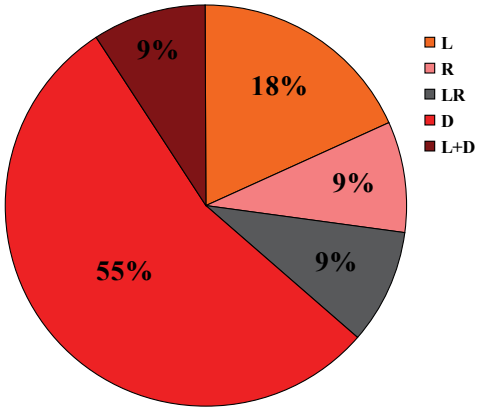


**Figure 4. Patterns of failure**
L – Local recurrence; R – Regional recurrence; LR – Locoregional recurrence; D – Distant metastases; L+D – Locoregional recurrence and distant metastases

The LR-RFS rate at 2 years was 66.6% (Figure 5). The median duration of LR-RFS was 15 months (range: 0-50). The DM-RFS rate at 2 years was

65.7% (Figure 5). The median duration of DM-RFS was also 15 months (range, 4-50). The OS rate at 2 years was 57.2% (Figure 5). The median duration of OS was 20 months (range: 7-50). There was no significant difference in LRR-FS, DMR-FS, and OS between patients treated with postoperative radiotherapy and those treated with definitive radiotherapy with or without concurrent chemotherapy (Figure 6, Figure 7, and Figure 8, respectively).

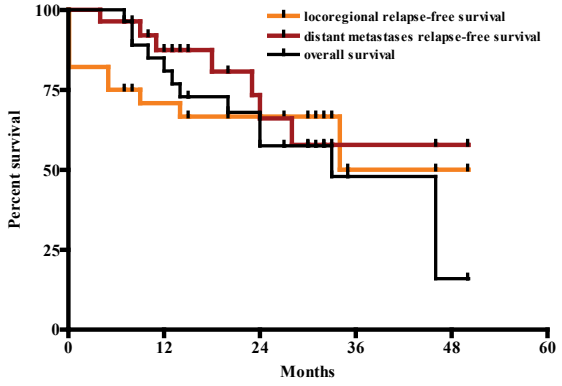


**Figure 5. Kaplan-Meier plots of survival**

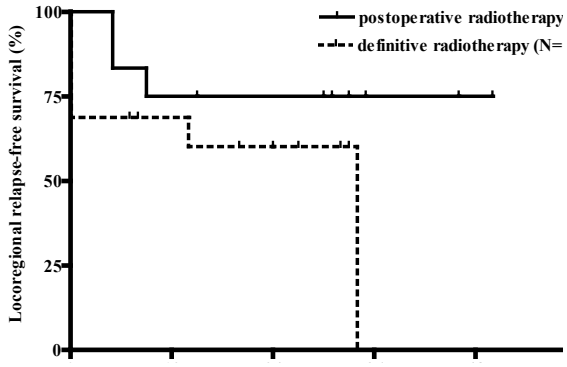


**Figure 6. Kaplan-Meier curves of locoregional relapse-free survival by type of radiotherapy. Log-rank test; $\chi^2$= 1.855; p= 0.1733.**

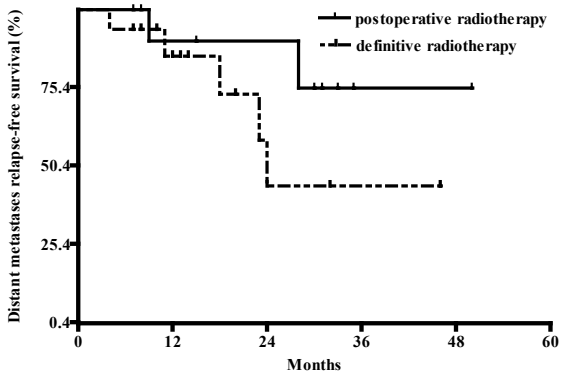


**Figure 7. Kaplan-Meier curves of distant metastases relapse-free survival by type of radiotherapy. Log-rank test; $\chi^2$= 1.716; p= 0.1902.**

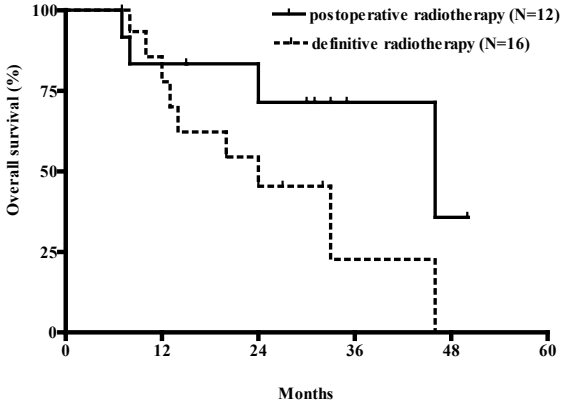


**Figure 8. Kaplan-Meier curves of overall survival by type of radiotherapy. Log-rank test; $\chi^2$= 2.694; p= 0.1007.**

## CONCLUSION

Head and neck cancer among young patients is relatively rare disease. Endogenous and exogenous factor associated with this disease in this age group of patients remains unknown. Research, in previous 30 years, has been to some extent, contradictory, because different series have reported different and sometimes, controversial results regarding stage, onset of disease and prognosis. The most common pattern of failure in our series of patients was distant metastasis and it is in line with case series published in the past decade (22-24). The low incidence of head and neck carcinoma in this subgroup of young adults has made development of prospective studies difficult. Multi-institutional collaboration must be encouraged in order to conduct prospective randomized studies, which would result in an unbiased data. HPV screening and unidentified genetic factors could be the area of potential research field, which will lead to narrowing population scope of onset of this cancer among this group of patients. Identifying prognostic factors in this subgroup of patients, will give possibility to individualize treatment, which will lead to better control of this disease in the future. Introduction of new target therapies, innovative regimes in fractionated radiation and application of newly developed radiotherapy techniques, could lead to higher healing rate and better prognosis in this subset of patients with improving quality of life (25-27).

### Conflict of interest

We declare no conflicts of interest.

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