

Definitive Intensity-modulated Radiation Therapy in Elderly Patients with Locally Advanced Oropharyngeal Cancer

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Abstract. *Background:* To evaluate the treatment tolerance and clinical outcomes in patients aged 70 years and older with locally advanced oropharyngeal cancer treated by definitive intensity-modulated radiation therapy (IMRT). *Patients and Methods:* We retrospectively analyzed 15 consecutive elderly patients, with histologically-proven squamous cell carcinoma of the oropharynx, staged T3-4 with or without involved lymph nodes at diagnosis, who received definitive sequential IMRT (70 Gy; 2 Gy/fraction). Adult Comorbidity Evaluation-27 (ACE-27) score was calculated and its influence on treatment tolerance and clinical outcomes was analyzed. *Results:* A total of 15 patients were included with a median age of 77 years (range=70-88 years). At baseline, 8 patients (53.3%) had an ACE-27 score of 1, and the remainder (n=7, 46.7%) had a comorbidity index of 0. All patients completed programmed IMRT treatment, without any reduction of total dose. Oral pain and mucositis were the most common acute side-effects, classified as grade 3 in 6 patients (40%) only. Xerostomia was reported in 13 patients (86.7%), without severe manifestation. There was no hematological toxicity. ACE-27 score was not related to higher severe acute toxicity. No patients experienced grade 3 or more late toxicity. Five-year overall survival and disease-free survival rates were 63.6% (95% confidence interval=32.7-83.3%) and 55% (95% confidence interval=24.4-77.6%), respectively. Comorbidity score did not influence survival outcomes, both overall survival ($p=0.46$) and disease-free survival ($p=0.55$). *Conclusion:* Treatment tolerance, as well as survival outcomes were good in elderly

oropharyngeal cancer patients treated with definitive sequential IMRT. Due to age and comorbidity, no dose or volume reduction for IMRT should be considered in this setting of patients. A prospective randomized trial with a large sample size should be conducted to confirm our results.

Management of patients with oropharyngeal cancer is complex and requires multidisciplinary team involvement, especially in those with locally advanced stage disease. Over the years, the use of radiation therapy (RT) as primary treatment has markedly increased and the intensity-modulated technique (IMRT) is now the predominant application of RT used, due to its ability in optimizing dose distributions (1). Based on a large number of clinical trials showing significant increase in overall survival (OS), concomitant chemoradiotherapy (CRT) has become the standard treatment for locoregionally advanced oropharyngeal carcinoma (2). But CRT is still not considered as a standard of care for elderly patients. In fact, the vast majority of these randomized studies have not enrolled old (≥ 70 years) patients and the updated meta-analysis of chemotherapy in head and neck cancer (MACH-NC) did not show any survival benefit resulting from the addition of chemotherapy for elderly patients, suggesting that the real impact of CRT remains to be determined in this setting for these patients (2).

Therefore, we felt that a more detailed look at elderly patients could be of interest. We tested definitive sequential IMRT in elderly patients with locally advanced oropharyngeal cancer. The aim of this study was to report the long-term follow-up data. The acute and late adverse effects were also determined.

Patients and Methods

Patient population. We retrospectively analyzed data from all consecutive elderly patients with locally advanced oropharyngeal cancer treated by definitive RT from January 2009 to August 2014. The study was approved by the Institutional Reviewed Board (October 10 2016, P-443/2016) and patients signed an informed consent form. Selection criteria for analysis cases included the

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following patients: the elderly (≥ 70 years); those with newly diagnosed histologically proven squamous cell carcinoma of the oropharynx; those with clinical T3-4 disease, with or without involved lymph nodes and without distant metastasis at diagnosis; those without history of previous RT or chemotherapy. Patients' performance status was assessed by the Eastern Cooperative Oncology Group Performance Status (PS) score (3). The Adult Comorbidity Evaluation-27 (ACE-27) score, a 27-item validated comorbidity index specific for head and neck cancer, was used to analyze patient comorbidities (4).

Radiation therapy. RT was delivered using a standard fractionation at 2 Gy/fraction/day, 5 days/week, to a total dose of 70 Gy/35 fractions/7 weeks. Sequential IMRT technique was utilized. A total dose of 50 Gy was delivered to the low-risk target volume (sites of suspected subclinical spread), followed by the intermediate dose boost (60 Gy) to the entire anatomical subsite and the involved lymph node levels and highdose boost (70 Gy) to the primary tumor and pathological lymph nodes.

Follow-up. During RT, patients were examined daily. Once treatment ended, patients were evaluated at 6-week intervals for the first year, then every 3 months for the next 2 years, and every 6 months thereafter. Toxicity was evaluated using National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (5). Patients were followed-up closely to evaluate toxicities and detect persistent or recurrent disease by clinical and fiberoptic examinations; where appropriate computed tomography or magnetic resonance imaging was performed.

Statistical analysis. Statistical analysis was performed using RStudio-0.98.1091 software. Standard descriptive statistics were used to evaluate the distribution of each factor. Continuous data were given as median (range), and categorical data as the number of observations and ratios. Overall (OS) and disease-free (DFS) survival were calculated in months from the date of the end of RT to the date of the last follow-up, death (OS) and/or relapse (DFS).

Outcomes were estimated according to the Kaplan-Meier method and survival curves were compared using the log-rank test (6). In order to determine the influence on survival outcomes the variable ACE-27 was considered. Toxicity and compliance with treatment rates were also examined. The non-parametric Bernard test was used. Statistical tests were two-sided and *p*-values lower than 0.05 were considered significant.

Results

Patient characteristics. A total of 15 elderly patients were eligible for this analysis. Patient and tumor characteristics are listed in Table I. Ages ranged from 70 to 88 years, with a median of 77 years. At baseline, all patients had a PS score of 0, whereas eight patients (53.3%) had an ACE-27 score of 1, and the remainder (*n*=7, 46.7%) had a comorbidity index of 0. The vast majority of patients (*n*=13; 86.7%) had more than one positive regional lymph node at diagnosis.

Treatment compliance and toxicity. All patients received the prescribed total dose of IMRT. Overall, RT was interrupted

Table I. Patient and tumor characteristics.

Characteristic	Value
Median age (range), years	77 (70-88)
Gender, n (%)	
Male	9 (60)
Female	6 (40)
PS, n (%)	
0	15 (100)
1	0 (0)
ACE-27 score, n (%)	
0	7 (46.7)
1	8 (53.3)
Smoker, n (%)	
No	5 (33.3)
Current	7 (43.7)
Former	3 (20)
Primary tumor site, n (%)	
Tonsil	11 (73.3)
Soft palate	1 (6.7)
Base of tongue	3 (20)
Clinical tumor stage, n (%)	
T1-2	9 (60)
T3-4	6 (40)
Clinical nodal stage, n (%)	
N0-1	2 (13.3)
N2-3	13 (86.7)

for a mean period of 5 days for acute toxicity in two patients (13.3%).

All patients had acute toxicity associated with treatment. Details are shown in Table II. Mucositis and oral pain were the most common acute symptoms. In total, the incidence rate of any severe acute toxicity was 37.5% (*n*=9). Xerostomia was reported in 13 patients (86.7%), without severe manifestation. Six patients (40%) had tube feeding due to inadequate oral caloric intake. There were no life-threatening consequences. No significant difference in higher severe acute toxicity was found regarding ACE-27 score (0 versus ≥ 1).

Late RT treatment-related toxicity was assessed among surviving patients and involved the following conditions: xerostomia (*n*= 9), oral pain (*n*=1), dysgeusia (*n*=5), trismus (*n*=1), dysphagia (*n*=5), brachial plexus injury (*n*=1). There was no evidence of osteoradionecrosis, nor of ototoxicity. None experienced grade 3 or more late toxicity.

Clinical outcomes. Overall, six patients deaths were recorded, two (33.3%) from conditions unrelated to cancer. The 2- and 5-year OS rates were 72.7% (95% CI=42.5-88.8%) and 63.6% (95% CI=32.7-83.3%), respectively (Figure 1). Locoregional recurrence was recorded in 2 patients (13.3%) and only one patient (6.7%) presented distant metastasis to lung. Two- and 5- year DFS were estimated at 66% (95% CI=36.5-84.3%) and 55% (95% CI=24.4-77.6%), respectively

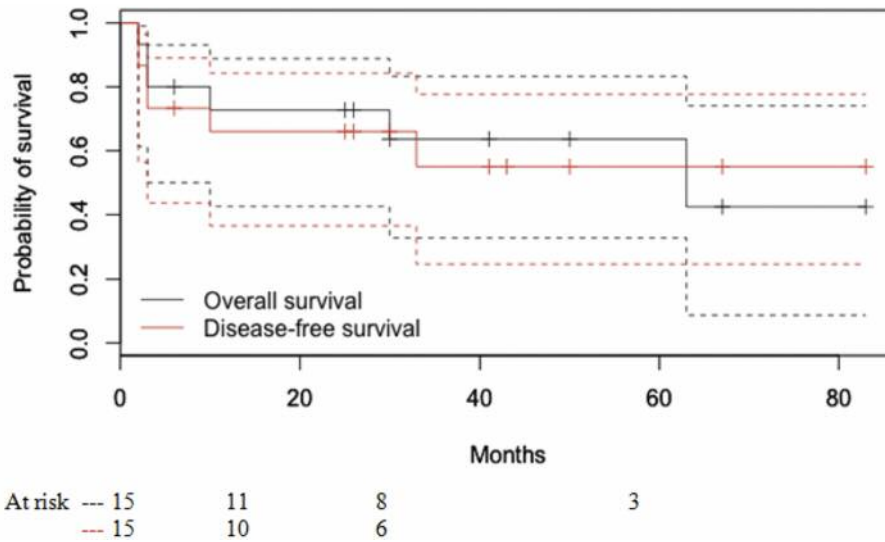


Figure 1. Kaplan-Meier curves of overall survival and disease-free survival of elderly patients after intensity-modulated radiation therapy.

Table II. Acute toxicity experienced by elderly patients after intensity-modulated radiation therapy.

Toxicity	Grade 1-2				Grade 3-4			
	ACE-27 score, n (%)			p-Value	ACE-27 score, n (%)			p-Value
	All (%)	0 (%)	1 (%)		All (%)	0 (%)	1 (%)	
Dermatitis radiation	1 (6.7)	1 (14.3)	-	0.63	1 (6.7)	-	1 (12.5)	0.73
Mucositis oral	11 (73.3)	4 (57.1)	7 (87.5)	0.66	4 (26.7)	3 (42.9)	1 (12.5)	0.42
Odinophagia/oral pain	13 (86.7)	6 (85.7)	7 (87.5)	0.97	2 (13.3)	1 (14.3)	1 (12.5)	0.97
Xerostomia	13 (86.7)	5 (71.4)	8 (100)	0.76	-	-	-	-
Dysgeusia	13 (86.7)	5 (71.4)	8 (100)	0.76	-	-	-	-
Dysphagia	6 (46.2)	3 (42.9)	3 (37.5)	0.96	2 (13.3)	2 (28.6)	-	0.72
Dysphonia	3 (20)	3 (42.9)	1 (12.5)	0.42	-	-	-	-
Neutrophil count decreased	1 (6.7)	-	1 (12.5)	0.73	-	-	-	-

ACE-27: Adult comorbidity index-2.

(Figure 1). ACE-27 score had no influence on survival outcomes. A 75% (95% CI=31.5-93.1%) 2-year survival was recorded in patients with ACE-27 score 0 and 71.4% (95% CI=25.8-0.92) in patients with ACE-27 score 1 ($p=0.46$). In 2-year disease free survival probabilities comparable results were found (75% versus 57.1%, respectively; $p=0.55$)

Discussion

This study provided a reliable evaluation of the effect of sequential IMRT in elderly patients with locally advanced oropharyngeal cancer. Results suggested that definitive IMRT with standard fractionation was effective in reducing mortality and both local and distant recurrences, without

deleterious effect on compliance and toxicity. The ACE-27 score was not related to survival and toxicity rates.

Although approximately 25% of patients with head and neck cancer are aged 70 years and over, over the past decade elderly patients have represented fewer than 10% of clinical trial participants (7, 8). This under-representation of the elderly suggests that it is necessary to better understand age-based differences in presentation, response to therapy and prognosis. Further studies should be designed exclusively for elderly patients. It is expected that they have similar comorbidities that could affect compliance with or response to treatment. Evaluation and quantification of comorbidity is paramount to stratifying elderly patients into groups with similar pre-treatment health condition that impacts on short-

term mortality and the ACE-27 index is an established tool in head and neck squamous cell carcinoma assessment (8, 9). Interestingly, our results showed no significant differences in clinical outcomes, toxicity manifestation and compliance with IMRT. This favorable profile could be explained by the good performance of the enrolled patients. In fact, a clear distinct impact of the ACE-27 severity scores was shown here. Our results are in agreement with survival rates found in the study of Datema *et al.*, in which the 2-year survival probability of a patient with ACE-27 score 1 was 67% against 75% for a patient with ACE-27 score 0 (9). To our knowledge, in the head and neck cancer scenario, there is only one published prospective study that required an age from 65 to 79 years (10). However, this study was performed to assess the efficacy and safety profiles of the induction chemotherapy, and did not contain enough RT data to allow a proper comparison of results. Based on five trials of the European Organization for Research and Treatment of Cancer restricted to patients receiving RT for head and neck cancer, Pignon *et al.* analyzed locoregional control, survival and side-effects in relation to the age of the patients (11). Globally, 1,589 patients were enrolled and 185 patients were over 70 years (11.6%). Although under-represented, the absolute number of elderly patients was considered sufficient to perform the analysis. Overall, acute RT tolerance was worse in elderly patients than younger patients, whereas there were no differences in term of local control and OS between age groups. The authors concluded that an age limit was not a good strategy to guide administration of head and neck cancer therapy. However, there are two main considerations. Firstly, their study had no information regarding comorbidity. Secondly, patient data were from 1980 to 1995 and tolerance rates may have been negatively influenced by RT technique. Recently, Nguyen *et al.* presented a series of 27 patients with locally advanced head and neck cancer aged ≥ 70 years treated with concurrent CRT (12). Only 11 cases had primary oropharyngeal neoplasia but no subgroup analysis for anatomic sites was available. The 2-year OS of the entire elderly cohort was 67.5%. In total, 16 patients developed grade 3 or more acute mucositis, seven had grade 3 or more hematological toxicity, five had severe skin reaction and three presented severe vomiting. The mean treatment break was 7 days. Our patients experienced a less severe toxicity profile and we believe this was because IMRT was not combined with chemotherapy. Moreover, if we compare results, our survival rate was better, but due to the short follow-up (median 12 months) observed by Nguyen *et al.*, no definitive conclusions can be drawn.

Our study could be useful to identify the optimal therapeutic strategy in elderly patients with locally advanced oropharyngeal cancer. The use of sequential IMRT appears to be safe and efficacious. Our employed RT fractionation schedule is justified by radiobiological research and clinical data. It has been well

demonstrated that hyperfractionation with dose escalation results in consistent survival benefit with an increase of severe acute side-effects, especially mucosal toxicity, compared with conventional fractionation (13-15). On the other hand, shortening the overall treatment time using accelerated fractionation improves locoregional control, but acute and late toxicities are also increased (16). Moreover, a recent meta-analysis showed an absolute survival benefit for altered fractionation of 3.4% at 5 years, but this benefit was limited to patients younger than 60 years of age (17). Therefore, considering that a consensus regarding hyperfractionation and altered fraction schedules has not yet emerged, and considering patient age and comorbidity, the higher toxicity risk outweighed the survival advantage and thus the conventional fractionation was chosen. In addition, the application of the IMRT technique was useful in reducing late toxicity, by sparing closely adjacent critical anatomic structures, such as salivary glands, pharyngeal constrictor muscles, mandible, temporomandibular joint and masticatory muscles.

However, our results should be viewed with caution. The retrospective nature of this analysis is the main limitation of the study. The sample size was relatively small, making results less robust. But homogeneity in the patient population and in the treatment approach, without missing data, represent the study strengths. Considering the lack of literature evidence on treatment recommendations for older patients with locally advanced oropharyngeal cancer, this study could be useful to assist the radiation oncologist in elderly patient counseling and clinical decision-making.

Conclusion

No general consensus exists for appropriate treatment in elderly patients with oropharyngeal cancer. A high degree of locoregional and distant control can be achieved with definitive sequential IMRT, with high compliance and tolerable toxicity. The definitive sequential IMRT technique should be considered a valid option in this patient setting. Further studies are paramount to confirm that elderly patients can benefit from this treatment approach.

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