# Efficacy and survival rate of intensity-modulated radiotherapy combined with chemotherapy for elderly patients with locally advanced oropharyngeal cancer

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**Abstract.** The efficacy of intensity-modulated radiotherapy (IMRT) combined with chemotherapy in the treatment of elderly patients with locally advanced oropharyngeal cancer and its effect on survival rate were studied. Elderly patients (n=150) diagnosed with locally advanced oropharyngeal cancer by histopathology were selected and randomly divided into the observation group (n=75) and the control group (n=75). Patients in the observation group were treated with IMRT combined with chemotherapy, while those in the control group were treated with conventional radiotherapy and chemotherapy. The two groups were treated with docetaxel + cisplatin (TP regimen). All patients received 1 to 2 cycles of docetaxel + cisplatin-induced chemotherapy, and after the radiotherapy began, the chemotherapy with docetaxel was synchronously conducted. The recent efficacy (tumor regression condition was observed at 3 months after the treatment), 1-year, 3-year and 5-year overall survival (OS), local-regional control (LRC), progression-free survival (PFS), disease-free survival (DFS) and the incidence rate of adverse reactions of patients in the two groups were compared. In the observation group, 73 patients completed the radiotherapy and chemotherapy, while all the patients in the control group completed the treatments. The 1-year OS of the observation group and the control group was 97.3 and 85.3%, respectively. In the observation group, the 3-year LRC, OS, PFS and DFS of the observation group was 94.5, 91.8, 90.4 and 87.7%, respectively; the 5-year LRC, OS, PFS and DFS was 64.4, 56.2, 56.2 and 54.8%, respectively. In the control group, the 3-year LRC, OS, PFS and DFS was 86.7, 73.3, 82.7 and 68.0%, respectively; the 5-year LRC, OS, PFS and DFS were 54.7, 45.3, 44.0 and 56.7%, respectively. The differences were statistically significant (P<0.05). In the observation group, the number of leukocytes was decreased, and the incidence rates of acute oropharyngeal mucosa reaction and radiation dermatitis were significantly lower than those in the control group. The differences were statistically significant (P<0.05). In conclusion, IMRT combined with chemotherapy can improve the OS and the 3-year and 5-year LRC, PFS and DFS of elderly patients with locally advanced oropharyngeal cancer, reduce toxic and side effects, and improve patients' quality of life.

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## Introduction

In recent years, oropharyngeal cancer has accounted for ~1.3% of systemic malignant tumors and 4.2% of head and neck cancers. With the changes in people's eating habits and gradually increased pressure, the incidence rate continues to rise. The disease often occurs in men, especially in those aged 50-60 years or alcoholics. In addition, betel nut, human papillomavirus infection and other factors are related to the occurrence of oral cancer to a certain degree (1). At present, if the locally advanced oral cancer is only treated by surgical treatments, the specificity of its anatomical location and strong invasion will bring great difficulties to the operation, which not only causes severe postoperative trauma, but also greatly affects organ functions (2). However, if the disease is only treated with radiotherapy, the possibility of the recurrence of the disease is greater than that treated with surgery (3). In particular, if the routine radiotherapy or surgery was conducted in stage III and IV, the 5-year survival rate will be <40%.

With the promotion of intensity-modulated radiotherapy (IMRT), increasingly a comprehensive treatment, IMRT combined with chemotherapy (4-6) has been proposed. IMRT has a certain targeting ability, so it can accurately act on the tumor target region, which ensures the function of normal tissues, and optimizes the dose on the target region (7).

## Patients and methods

*General data*. Patients (150) were numbered from 1-150 in order, and were randomly divided into the observation group

Table I. Comparison of general data between two groups of patients.

| Patient characteristics | Observation group n (%) | Control group n (%) | Statistics | |
|---|---|---|---|---|
| | | | $\chi^2$ | P-value |
| No. of patients | 75 (50.0) | 75 (50.0) | | |
| Sex | | | 0.234 | 0.772 |
| Male | 63 (84.0) | 65 (87.7) | | |
| Female | 12 (16.0) | 10 (13.3) | | |
| Age (years) | | | 0.503 | 0.766 |
| 40-60 | 54 (72.0) | 51 (68.0) | | |
| >60 | 21 (28.0) | 24 (32.0) | | |
| Location of lesion | | | 0.266 | 0.875 |
| Amygdala | 43 (57.3) | 41 (54.7) | | |
| Root of tongue | 20 (26.7) | 25 (33.3) | | |
| Soft palate | 12 (16.0) | 9 (12.0) | | |
| Clinical stage | | | 0.192 | 0.741 |
| Stage III | 34 (45.3) | 40 (53.3) | | |
| Stage IV | 41 (54.7) | 35 (46.7) | | |
| Pathological type | | | 0.258 | 0.813 |
| Low-undifferentiated squamous cell carcinoma | 45 (60.0 | 41 (54.7 | | |
| Moderate-high differentiated squamous cell carcinoma | 30 (40.0 | 34 (45.3 | | |
| Karnofsky Performance Score (KPS) | | | 0.791 | 0.952 |
| >90 | 48 (64.0) | 50 (66.7) | | |
| 70-90 | 24 (32.0) | 23 (30.7) | | |
| <70 | 3 (4.0) | 2 (2.7) | | |

and the control group using a computer. The implementation of treatment was conducted by following the principle of the single-blind trial. General data of two groups of patients are shown in Table I, and the differences were not statistically significant. The study was approved by the Ethics Committee of Shandong University Affiliated Jinan Central Hospital.

*Methods*

*Inclusion criteria*. i) Patients aged ≥40 years; ii) patients newly diagnosed with oral cancer by pathology; iii) patients who were divided into stage III-IV according to the Union for International Cancer Control (UICC) 2010 staging system (8); iv) patients with normal lung, liver and kidney functions before the treatment; v) patients without any contraindications to radiotherapy and chemotherapy; vi) patients whose stages were clearly determined by computed tomography (CT) and magnetic resonance imaging (MRI) before operation, and patients with distant metastasis were excluded; vii) patients with no other second primary tumor; viii) patients who signed the radiotherapy informed consent.

*Exclusion criteria*. i) Pregnant or lactating women; ii) patients complicated with severe infection; iii) patients with a second primary tumor; iv) patients complicated with heart, lung, liver, kidney or other organic diseases.

*Treatment methods*

*Grouping regimens*. After the induction chemotherapy, two groups of patients received concurrent radiotherapy and chemotherapy. The radiotherapy method in the observation group was IMRT, and that in the control group was conventional radiotherapy.

*Chemotherapy regimens*. i) Induction chemotherapy: On D1, 135 g/m$^2$ docetaxel was intravenously instilled for 1 h; on D2, cisplatin 75 mg/m$^2$ was intravenously instilled for 1 h; a cycle included 21 days, and there were 4 treatment cycles in total. ii) Concurrent chemotherapy: Patients were administered 20 mg/m$^2$ once a week for 6 weeks.

To avoid an allergic reaction, patients were given 20 mg dexamethasone at 6 and 12 h before administration, respectively. They took orally 50 mg diphenhydramine and were intravenously injected with 300 mg cimetidine at 30 min before administration.

*IMRT*. After the mask was fixed, the CT simulation was used to scan the images, which were transmitted to the planning system. After three-dimensional reconstruction and fusion by the three-dimensional reverse planning system, the IMRT program was formed. After the dose was verified, and the program was co-examined by physicians at three levels, the radiotherapy could be conducted.

*Conventional radiotherapy*. The dose was 2.12 Gy/fraction/day, and the frequency was 5 times/week. The total dose was 70 Gy. The radiotherapy was conducted for 33 times in total.

*Evaluation of efficacy and adverse reactions*. Evaluation of tumor depression: The Positron Emission Tomography (PET)

Table II. Comparison of the recent efficacy.

| Treatment efficacy | Observation group, n (%) | Control group, n (%) | P-value |
|---|---|---|---|
| Primary lesion | | | 0.556 |
| CR | 65 (89.1) | 64 (85.3) | |
| PR | 8 (10.9) | 11 (14.7) | |
| Cervical lymph node metastasis lesion | | | 0.248 |
| CR | 50 (71.4) | 52 (72.2) | |
| PR | 20 (28.6) | 20 (27.8) | |

CR, complete remission; PR, partial remission.

Response Criteria in Solid Tumors (PERCIST) was used according to the results of imageological review at 3 months after the treatment (9). Evaluation of adverse reactions in the acute phase: The National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) 4.0 was used (10). Evaluation adverse reactions in the distant phase: Criteria of Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) were jointly used to assess the radiation damage. According to these criteria, the adverse reactions were divided into 0-IV degree, and toxic and side effects were recorded once a week.

Follow-up began from the time of diagnosis. At 1 year after the diagnosis, patients were followed up and reviewed once every 3 months; at 2-5 years after the diagnosis, patients were followed up and reviewed once every 6 months. Main examinations: three routine examinations, oropharynx and neck MRI, chest and abdomen CT, pharynx fiberoptic bronchoscopy. T [overall survival (OS)] = T (death of patients/end of follow-up) - T (diagnosis); 3-year local-regional control (LRC) = the number of cases with no enlarged tumor confirmed by the imageological examination/the number of total cases; T (progression-free survival (PFS) = T (tumor recurrence/metastasis) - T (diagnosis); T [disease-free survival (DFS)] = T (no recurrence/metastasis) - T (end of diagnosis).

*Statistical analysis*. Data were processed using SPSS 21.0 (IBM, New York, NY, USA). The t-test was used to detect measurement data, $\chi^2$ test was used to detect enumeration data, and the Kaplan-Meier method was used to calculate the survival rate. The Kolmogorov-Smirnov (K-S) non-parametric test was used to compare the percentage. P<0.05 represents the statistically significant difference.

## Results

*Completion of treatment*. Seventy-three patients in the observation group completed the treatment, in which 1 patient did not complete the treatment and died, and 1 patient was lost to the follow-up. Cervical lymph node metastasis occurred in 70 patients. In the control group, all the patients completed the treatment, and cervical lymph node metastasis occurred in 72 patients.

*Comparison of the recent efficacy*. At 3 months after the radiotherapy, imageological examination was conducted for the two groups of patients, the primary lesion and cervical lymph node metastastatic lesions were determined, which showed that complete remission (CR) was achieved in primary lesions of 67 patients (89.3%), and partial remission (PR) was achieved in 8 patients (00.7%) in the observation group. CR was achieved in cervical lymph node metastasis lesions of 50 patients (70.4%), and PR in 21 patients (29.6%). In the control group, CR was achieved in primary lesions of 64 patients (85.3%), and PR in 11 patients (14.7%). CR was achieved in cervical lymph node metastasis lesions of 51 patients (72.9%), and PR in 19 patients (27.1%). As shown in Table II, there was no significant difference in the recent efficacy between the two groups.

*Comparison of the survival rate between the two groups*. In the observation group, 1-year LRC, OS, PFS and DFS was 97.3, 97.3, 95.9 and 95.9%, respectively; 3-year LRC, OS, PFS and DFS was 94.5, 91.8, 90.4 and 87.7%, respectively; 5-year LRC, OS, PFS and DFS was 64.4, 56.2 56.2 and 54.8%, respectively. In the control group, 1-year LRC, OS, PFS and DFS was 92.0, 85.3, 92.0 and 76.0%, respectively; 3-year LRC, OS, PFS and DFS was 86.7, 73.3, 82.7 and 68.0%, respectively; 5-year LRC, OS, PFS and DFS was 54.7, 45.3, 44.0 and 56.7%, respectively. The differences in 3-year and 5-year LRC, OS, PFS and DFS between the observation group and the control group were statistically significant (P<0.05 for all comparisons), and 5-year LRC, OS, PFS and DFS were significantly decreased compared with 1-year and 3-year LRC, OS, PFS and DFS. The details of the survival rate of the two groups are shown in Table III.

*Comparisons of adverse reactions*. As shown in Table IV, leukocytes were decreased to different degrees in patients of the observation group and the control group during the whole treatment. The adverse reactions were mainly concentrated in the I-II degree, including oropharyngeal mucosa reaction and radiation dermatitis. The adverse reactions in the observation group were reduced compared with those in the control group (P<0.05 for all comparisons).

## Discussion

According to the survey data over the past years, the incidence rate of oropharyngeal cancer is gradually increasing, which often occurs in the 50-60-year-old males, especially in those addicted to alcohol and tobacco (10). For oropharyngeal cancer in the stage III-IV, the difficulty of surgery is much higher, in which there will be more cancer tissues left. Therefore, the preferred choice is radiotherapy and chemotherapy, and the primary problem of radiotherapy and chemotherapy is how to kill cancer cells farthest while improving the quality of life of patients (11). Induction chemotherapy, that is, pre-radiotherapy chemotherapy, whose efficacy is not affected by radiotherapy, easily plays a role at the tumor site, improves the radiation sensitivity, eliminates subclinical lesions and improves the survival rate of patients. The side effects of radiotherapy have a great impact on the quality of life of patients. With the development and application of computer technology, the IMRT has been proposed, and side effects such as xerostomia are expected to

Table III. Comparison of the survival rate between the two groups.

| | Stage III | | | Stage IV | | |
|---|---|---|---|---|---|---|
| Survival rate | Observation group (n=33) | Control group (n=40) | P-value | Observation group (n=40) | Control group (n=35) | P-value |
| LRC, n (%) | | | | | | |
| 1-year | 33 (100.0) | 38 (95.0) | 0.042 | 38 (95.0) | 31 (88.6) | 0.022 |
| 3-year | 32 (97.0) | 36 (90.0) | 0.037 | 37 (92.5) | 29 (82.9) | 0.021 |
| 5-year | 25 (75.8) | 26 (65.0) | 0.017 | 22 (55.0) | 15 (42.9) | 0.027 |
| OS, n (%) | | | | | | |
| 1-year | 32 (97.0) | 37 (92.5) | 0.078 | 38 (95.0) | 27 (77.1) | 0.019 |
| 3-year | 31 (94.0) | 30 (75.0) | 0.011 | 36 (90.0) | 25 (71.4) | 0.014 |
| 5-year | 23 (69.7) | 22 (55.0) | 0.036 | 18 (45.0) | 12 (34.3) | 0.028 |
| PFS, n (%) | | | | | | |
| 1-year | 32 (97.0) | 37 (92.5) | 0.049 | 37 (92.5) | 30 (85.7) | 0.039 |
| 3-year | 32 (96.7) | 35 (87.5) | 0.038 | 34 (85.0) | 27 (77.1) | 0.032 |
| 5-year | 20 (60.6) | 20 (50.0) | 0.019 | 21 (52.5) | 13 (37.1) | 0.014 |
| DFS, n (%) | | | | | | |
| 1-year | 32 (97.0) | 32 (80.0) | 0.044 | 38 (95.0) | 25 (71.4) | 0.027 |
| 3-year | 30 (90.1) | 28 (70) | 0.019 | 34 (85) | 23 (65.7) | 0.015 |
| 5-year | 21 (63.6) | 23 (57.5) | 0.034 | 19 (47.5) | 12 (34.3) | 0.036 |

LRC, local-regional control; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival.

Table IV. Comparisons of adverse reactions between the two groups.

| | Observation group (n=73) | | | Control group (n=75) | | | |
|---|---|---|---|---|---|---|---|
| Toxic reaction | 0 | I-II | III-IV | 0 | I-II | III-IV | P-value |
| Decreased leukocytes | 4 (5.5) | 38 (52.1) | 31 (42.5) | 4 (5.3) | 56 (74.6) | 15 (20.0) | 0.027 |
| Xerostomia | 0 0 | 57 (78.1) | 16 (21.9) | 0 0 | 67 (89.3) | 8 (1.1) | 0.018 |
| Radiation dermatitis | 0 0 | 49 (67.1) | 24 (32.9) | 0 0 | 55 (73.3) | 20 (26.7) | 0.044 |

be improved (12,13). IMRT has several radiation fields, and the intensity of each sub-field can be adjusted. After precise adjustment, tumor regions are high-dose irradiation area, and the surrounding normal tissues and organs are low-dose irradiation areas, which maintain the function of normal tissues and organs to the maximum degree and improve the quality of life of patients while improving the LRC of tumor (7). In this study, the difference in efficacy between IMRT and radiotherapy combined with chemotherapy is emphasized. The results showed that both the 1-year and 3-year LRC in the observation group were higher than those in the control group, and the same is true in the toxic and side effects, which are consistent with the study findings of Huang *et al* (14) and Daly *et al* (15).

In order to reduce the random error, the patients were randomly divided into groups using a computer in this study. In the course of treatment, only the researchers knew the treatment plan, but the patients themselves did not know the plan, which reduced the influence of their subjective consciousness on the data collection in the experiment, thus making the follow-up more reliable. Although the impact of subjective awareness of the researchers on test results was not reduced, the safety of patients in the test was ensured. In the comparison of the survival rate, staging was conducted for patients to compare the difference in the survival rate between the observation group and the control group. Except the differences in a few indicators between the two groups they were not statistically significant, other significant differences suggested that the efficacy of the observation group is better than that of the control group. However, since there were 33 patients in stage III and 40 patients in stage IV in the control group, and there were 40 patients in stage III and 35 patients in stage IV,

the test results were not universal, so in order to study the effect of staging on the survival rate, the number of study objects should be increased. In view of the fact that the second primary tumor exerts an unknown detrimental effect on the long-term efficacy, patients with a second primary tumor were excluded during inclusion so as to make the results comparable (16).

There are many regimens for induction chemotherapy. Vermorken *et al* (17) believed that the efficacy of docetaxel + cisplatin + 5-fluorouracil (TPF) regimen (docetaxel + cisplatin + 5-fluorouracil docetaxel + cisplatin + 5-fluorouracil) for induction chemotherapy is increased compared with that of the cisplatin + 5-fluorouracil (PF regimen); Rosenthal *et al* (18) proposed the concurrent platinum-based chemotherapy. The super-segmented IMRT has also been put forward, it combines the advantages of super-grading with those of IMRT. The study of Monnerat *et al* (16) showed the feasibility of this regimen, but stage II tests are still needed to validate its efficacy (19). The assessment of survival and adverse reactions was limited by only using the criteria of the World Health Organization (WHO), Response Evaluation Criteria In Solid Tumors (RECIST) and RECIST 1.1, especially when assessing the efficacy of newer cancer treatments. These criteria needed to be further revised and enhanced after being verified by various diseases and treatments (20). Hoeller *et al* (21) argued that the late effects of normal tissue-subjective, objective, management, and analytic (LENT-SOMA) scoring system is superior to the RTOG criteria, so we need to consider optimizing the LENT/SOMA scoring system, thus making the report on advanced radioactive morbidity rate more standardized (21). Differently, the latest study of Kelly *et al* (22) revealed that the treatment regimen not modulated by intensity can be applied to reduce the occurrence of side effects, such as reducing radiation dose and replacing radiation-sensitive chemotherapy.

In conclusion, IMRT combined with chemotherapy can be used to improve the OS of elderly patients with locally advanced oropharyngeal cancer, 3-year and 5-year LRC, PFS and DFS, reduce side effects and improve patients' quality of life.

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