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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**ANALYSIS OF THE SIGNIFICANCE OF COMBINED
SURGICAL AND CONSERVATIVE TREATMENT FOR T3
STAGE III LARYNGEAL CANCER**

Specialty: 3224.01 - “Oncology”

Field of science: Medicine

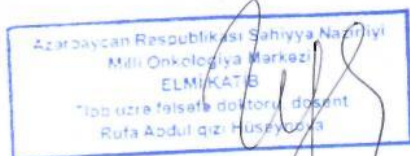
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The work was performed at the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

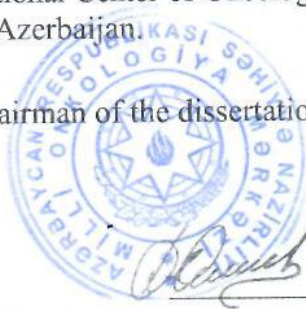
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INTRODUCTION

The relevance of the topic.

Laryngeal cancer (LC) is one of the most common oncological disease and it ranks 5-6th place in the world in terms of prevalence with an incidence of 2.8%¹. This disease is more common in men, especially between the ages of 65-75 years, and in women - between the ages of 70-80². In 2011, the American Cancer Society estimated that approximately 12,740 patients were diagnosed with laryngeal cancer in the United States. Mortality rates vary depending on the location and stage of the early tumor. Geographic diversity, lifestyle and harmful habits of the population, as well as other environmental factors play an important role in the distribution of disease rates and anatomical localization^{3,4}.

Among the countries of the Commonwealth of Independent States, the prevalence of laryngeal cancer in Azerbaijan is 1-2%. In the Republic of Azerbaijan, approximately 400/100,000 people have inflammatory and tumor diseases of the larynx.

The 5-year life expectancy of patients treated for laryngeal cancer is 92% for stage I, 80% for stage II, and 67% for stage III.⁵

The risk of recurrence is high in the first 2-3 years in patients treated for laryngeal cancer. After 5 years, the risk of recurrence is rare and is usually associated with the main new malignancy. Unfortunately,

¹ Əliyev, Əziz. Baş və boyun şişlərin cərrahi müalicəsi: dərslik / Ə.Əliyev. – Bakı. – 2015, - 215

² Ольшанский, В.О. Проблема рака гортани на страницах «Вестника оториноларингологии» / В.О.Ольшанский, И.В.Решетов, С.В.Томина // Вестник оториноларингологии, - 2006, №5, - с. 56-59.

³ Пачес, А.И. Опухоли головы и шеи: Клиническое руководство / А.И.Пачес. - 5-е изд. - М., - 2013,- с. 244-274.

⁴ Раджабова, З.А.-Г. Распространенный рак гортани: Обзор литературы / З.А.-Г.Раджабова, М.А.Котов, М.А.Эберт [и др.] // Сибирский онкологический журнал, - 2019, т.18, №5, - с. 97-107.

⁵ Чойнзонов, Е.Л. Рак гортани в Томской области: оценка онкологической помощи на основе показателей выживаемости (2004-2013 гг.) / Е.Л.Чойнзонов, Л.Ф.Писарева, Л.Д.Жуйкова[и др.] // Вопросы онкологии, - 2014, т.60, №6, - с. 683-686

most patients are admitted to the hospital at stage III-IV. Since it is already in the late stage in these patients, the neoplasms invades anterior and posterior commissure, the mucous membrane of the laryngeal cartilages, causes shortness of breath and suffocation^{6,7}.

According to a number of studies, radiochemotherapy is considered an effective treatment method for T3, III stage laryngeal cancer. In T3, III stage subglottic cancer, radiotherapy can be complicated by acute stenosis. For this reason, in such cases, laryngectomy surgery is performed first, and during the operation, 5-6th tracheal semicircular rings are removed. If necessary, neck dissection is performed. Approximately 4-6 weeks after the surgery, radiotherapy is performed. Also, the possibility of developing pharyngocutaneous fistula, bleeding complications, and skin necrosis is relatively low in patients who received radiotherapy after surgery, compared to patients who received only primary conservative (radio-chemotherapy) treatment. Usually, such complications can prolong the hospital stay of patients. In some cases, if recurrence occurs only after conservative treatment, laryngectomy surgery should be performed^{8,9,10}.

At present, combined treatment is recommended for T3, stage III laryngeal cancer: total laryngectomy + lymphodissection and radiotherapy, or if extracapsular spread in cervical lymph nodes occurred, post-operative radiochemotherapy (RCT) is recommended. Polychemotherapy also increases the effectiveness of radiotherapy. In some cases, concomitant disease in patients play an important role

⁶ Пачес, А.И. Опухоли гортани. Опухоли головы и шеи / А.И.Пачес, Е.Г.Матякин - 5-е изд., доп. и перераб. М.: Практическая медицина, - 2013, - с. 182-185.

⁷ Əmirəliyev, Namiq. Baş-boyun şişləri: dərslik / Namiq Əmirəliyev, Azər Əmirəslanov. – Bakı – 2012, - 436 s.

⁸ Kaur, P. Combined hyperthermia and Radiotherapy for the treatment of Cancer / P.Kaur, M.D.Hurwitz, S.Krishnan [et al.] // Cancers, - 2011, v.3, - p. 3799-3823.

⁹ Чойнзонов, Е.Л. Современные методы лечения больных раком гортани и гортаноглотки / Е.Л.Чойнзонов, Ю.В.Белевич, С.Ю.Чижевская [и др.] // Сибирский онкологический журнал, - 2016, №3, с. 91-96.

¹⁰ Танеева, А.Ш. Спорные вопросы в лечении больных раком складочного отдела гортани Т3N0–2M0 / А.Ш.Танеева, А.М.Мудунов, С.Б.Алиева // Опухоли головы и шеи, - 2014, №2, - с. 10-13.

in delayed wound healing (tuberculosis, diabetes, ischemic heart disease- IHD) ^{11,12,13}.

The development risk of recurrence in patients underwent laryngeal cancer surgery and conservative treatment, the late stages of patients' application mostly result in tracheostomy, depending on the choice of treatment tactics may increase the mortality rate and for these reasons the scientific research may be considered relevant.

The purpose of the study

Study of the importance of conservative and combined treatment methods in order to improve the treatment results of patients with T3, III stage of laryngeal cancer.

Research objects

1. Comparative analysis of the effectiveness of radiotherapy after surgery (laryngectomy+lymphodissection) in T3, III stage laryngeal cancer.

2. Determination of performing lymphodissection at the T3, III stage laryngeal cancer, depending on the degree of regional spread of the process.

3. Analysis of the effect of the results of conservative therapy in T3, III stage laryngeal cancer.

4. Comparative analysis of complications after radiotherapy and surgical treatment (RRT+LE) in laryngeal cancer, especially formation of pharyngocutaneous fistula.

Research Methods

The study included 128 patients with T3N0-1M0 laryngeal cancer. The patients were divided into 4 groups depending on the treat-

¹¹ Панкратов, В.А. Современные возможности консервативного и комбинированного лечения местнораспространенного рака гортани / В.А.Панкратов, В.Г.Андреев, Ю.С.Мардынский[и др.] // Сибирский онкологический журнал, - 2013, №2(56), - с. 36-40.

¹² İsayeva, E.H. Qırtlaq xərcənginə görə laringektomiya əməliyyatından sonra səs funksiyasının bərpası // Sağlamlıq, - 2015, №3, - s. 181-184.

¹³ Чижевская, С.Ю. Качество жизни больных раком гортани и гортаноглотки на этапах комбинированного лечения и в отдаленные сроки / С.Ю.Чижевская, Е.Л.Чойнзонов, Л.Н.Балацкая// Сибирский онкологический журнал, - 2015, №2, - с. 15-22.

ment methods. The mortality, survival and cumulative survival rates of patients were analyzed using the actuarial method by constructing survival tables based on annual follow-up data (1 year interval).

The main provisions of dissertation

1. The priority treatment methods for patients with T3, III laryngeal cancer have been determined.

2. The surgical combined treatment method is considered the main method of choice in the complex treatment of T3, III laryngeal cancer patients.

3. Performing radiation therapy after laryngectomy significantly reduces the risk of development of pharyngocutaneous fistula, recurrence and metastasis.

Scientific novelty of study

For the first time in Azerbaijan, a comparative analysis of the effectiveness of combined surgical and conservative treatment methods was conducted in patients with T3, III laryngeal cancer. The surgical combined treatment method, as the most effective method in the treatment of patients with stage III laryngeal cancer, compared to conservative treatment, enabled to reduce the development of pharyngocutaneous fistula, relapses and metastases, as well as to increase the 5-year survival rates of patients, and to decrease the total mortality rates.

The theoretical and practical significance of the study

As a result of the research, the reduction of the risk of relapses and metastases during the combined surgical treatment, the improvement of the patient's survival rate and the prolongation of the remission indicate that this method is the main method of choice in the complex treatment of T3, III stage laryngeal cancer patients.

The study results broaden the understanding of the features of the structure of tumor pathologies of the larynx. An in-depth and comparative study of the material allows to determine the spread characteristics of malignant neoplasms of the larynx depending on a number of different characteristics that affect the clinical stage of the disease, as well as the characteristics of the tumor (the degree of differentiation of the tumor, the nature of tumor development, the ability to metastasize, radiation pathomorphosis).

Approbation of the dissertation and published works:

The main materials of the dissertation were presented at the scientific-practical conference dedicated to Antimicrobial treatment and clinical microbiology (Rostov-on-Don, 2018), at the congress of oncologists and radiologists of the CIS countries (2018 and 2021), at the interdepartmental conference of National Center of Oncology (Baku, 07 July 2022, protocol No. 4a), at the meeting of the Scientific seminar of the FD 1.02 Dissertation Council operating under NCO (Baku, 16 September 2022, protocol No. 5)

The main theoretical and practical provisions of the dissertation are mentioned in 13 published scientific works (10 articles, 3 abstracts). Scientific works on the topic of the study were published both in Azerbaijan (5 articles, 4 theses), and in foreign journals (1 article, 2 theses).

Application of the study.

The results of the research are used in the educational process and lectures at the Oncology Department of Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev, and in practical work at Department of Head and Neck Tumors of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The organization in which the dissertation is carried out

The study was carried out at National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan.

The volume and structure of the dissertation

The dissertation is presented on 133 pages of typewritten text (239.564 characters) consisting of an introduction (13.868 characters), chapter 1 and 2 - literature review (45.708 characters), chapter 4 - personal research (115.560 characters), results (23.965 characters), conclusions (2.314 characters), practical recommendations (3634 characters) and references (26.522 characters). The list of references includes 209 sources that most of them belong to the last 5-10 years. The dissertation contains 20 tables, 18 figures and 3 diagrams.

MATERIALS AND METHODS

The study included 128 patients with T3N01M0 laryngeal cancer who received conservative and surgical treatment at National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan in 2014-2017.

89.1% of patients with T3N0-1M0 laryngeal cancer were men (114 patients), and 10.9% were women (14 patients), which corresponds to the epidemiological data on the gender characteristics of the spread of laryngeal cancer in the Republic of Azerbaijan. The average age of the patients was 53.7 ± 1.02 years.

The patients were examined according to international standards. 128 patients diagnosed with laryngeal cancer were examined using a complex program and diagnostic algorithm. Factors such as localization of the tumor, nature of tumor development, laryngeal cartilage configuration and involvement in the process, tumor size, histological type of tumor, tumor infiltration into surrounding tissues were analyzed during the study.

A mixed tumor (46.9%), tumor in the glottis and supraglottis of larynx (52.4%), no disruption of laryngeal cartilage configuration (76.6%) intact of laryngeal cartilage configuration (76.6%), tumor size larger than 4 cm (75.8%), having a squamous cell structure (94.5%), absence of infiltration into the underlying and surrounding soft tissues (63.3%), absence of metastases to the regional lymph nodes (82.8%) were observed in patients.

To achieve the objectives, general clinical, laboratory and instrumental examinations were performed: clinical and laboratory tests, X-ray examination, ultrasound examination of the neck and areas with possible metastasis, and, if necessary, intravenous contrast and native computed tomography of the larynx, in some cases, magnetic resonance imaging to assess soft tissues, as well as radionuclide examination of skeletal bones.

In addition to the general clinical examination, instrumental examinations were performed in all patients - direct and indirect laryngoscopy, according to G. M. Zemtsov lateral neck radiography, if necessary - x-ray tomography of the larynx, examination of the respiratory

tract with the help of a BR-3 "Olympus" (Japan) flexible fiberoptic endoscope, as well as cytological and histological examinations of tumor biotates.

All patients with stage T3N0-1M0 laryngeal cancer underwent antitumor treatment with a radical program after comprehensive examination (with morphological differential diagnosis). Patients are divided into 4 groups depending on the treatment methods:

Group I consisted of 49 (38.3%) patients with T3N0-1M0 laryngeal cancer who received a split-course of remote radiation therapy (RRT): single source dose (SSD) 2 Gray, total source dose (TSD) up to 60 Gray in two mutualmode (RRT group).

Group II consisted of 46 patients (36.0%) with stage T3N0-1M0 laryngeal cancer. After laryngectomy (LE), a course of radical remote gamma-therapy (SSD- 2 Gr, TSD - up to 60 Gr in two mutual mode) was performed (LE+RRT group).

Group III consisted of 15 patients (11.7%), who received combined treatment: 2 courses of neoadjuvant polychemotherapy, regimen: on day 1 Cisplatin 80 mg/m² and on 1-5 days Fluoruracil 750 mg/m², TD 3750 - 5000 mg + RRTSSD 2 Gr TSD up to 40 Gr and 2 courses of adjuvant chemotherapy with the same protocol (PCT+RRT group).

Group IV consisted of 18 patients (14.0%) who received combined treatment: laryngectomy (LE)+remote radiotherapy SSD 2 Gr TSD up to 40 Gr + 2 courses of neoadjuvant intra-arterial chemotherapy: schedule - on day 1 Taxotere 75 mg/m² and Cisplatin 80 mg/m² (LE+ RRT+ PCT group).

The analysis and mathematical processing of the obtained results was carried out with the help of the "Microsoft Excel" program on a Pentium-166 MMX computer using various statistical functions.

The reliability of the differences in indicators abomg the groups was determined using the "Student" -Fisher test.

Indicators that differed from control indicators with a probability of 95% were considered reliable (P<0.05).

Life indicators of patients (death, recovery, cumulative life) were calculated by the actuarial method, by setting up life tables based on the data of annual observations (1-year intervals).

This method is known as the expert "Life-table" method (recommended by the International Union Against Cancer (UICC)).

RESEARCH RESULTS AND DISCUSSION

The results of RRT and LE+RRT in patients with T3N0-1M0 stage laryngeal cancer.

In study, 49 (38.3%) patients in the RRT group (I) received remote radiation therapy with a radical program (SSD 2 Gr TSD up to 60 Gr in two mutual mode), and 46 (36.0%) patients in the II group that underwent LE+RRT after radical laryngectomy received remote radiation therapy (SSD 2 Gr TSD up to 60 Gr in two mutual mode).

The majority of patients in both groups were men aged 51-70 years (61.3% and 65.3%, respectively). There were fewer women in terms of both the total number (8.2% and 8.7%, respectively) and the indicated age group (6.0% and 4.4%, respectively). Thus, both groups did not differ in terms of age and gender.

Analysis of tumor development and localization in different areas of the larynx showed that in both examined groups, patients with a mixed tumor (49.0% and 52.2%, respectively) prevailed. The tumor was most often located in the glottis of larynx (61.2% and 63%, respectively), spreading to supraglottis part of larynx. Thus, there was very little difference between groups I and II in terms of tumor growth and localization in different areas of the larynx.

The majority of patients in both groups (65.3% and 65.2%, respectively) had a tumor larger than 4 cm.

In terms of the extent of metastases, there were no metastases in both groups (T3N0M0) (77.6% and 84.9%, respectively). Regional lymph node metastases (T3N1M0) were detected in 11 (22.4%) patients in group I and 7 (15.1%) in group II.

The most common complications during surgery were wound necrosis and suppuration. The main reason for this was the lack of pharyngeal sutures, as well as formation of pharyngeal fistulas, pharyngospasm. These complications were observed in 4 patients. The most common causes of death in patients after laryngectomy were arrosive bleeding, pneumonia, purulent tracheitis. Death occurred in 1 patient.

In the study, the direct results of remote radiation therapy (RRT) and laryngectomy + remote radiation therapy (LE+RRT) treatment methods conducted in groups I and II were evaluated according to the degree of tumor regression. Observations have showed that complete tumor regression after radiation therapy was almost the same in both groups (40.8% and 41.3%, respectively). Partial tumor regression was recorded in 55.1% of patients in the RRT group and 43.5% of patients in the LE+RRT group. Treatment failure occurred in 4.1% of cases in group I and 15.2% in group II.

After total laryngectomy, the patients begin oral feeding and their breathing was provided by tracheostomy. The main disadvantage of this surgery is the loss of voice function and its restoration using logopedic methods is not always successful. Depending on the treatment method, the recurrence rate and incidence of metastases, duration of development were different in the patient groups. Recurrence and metastases were more likely to develop after RRT (59.1%) than after LE+RRT (13.0%). Thus, recurrence occurred in 14 (28.5%) patients after remote radiation therapy, and metastases occurred in 15 (30.6%) patients, and after LE+RRT, respectively it was observed in 1 (2.2%) and 5 (10, 8%) cases (table 1).

The analysis of incidence rate of recurrence and metastases have shown that recurrence and metastases occurred mostly within 1-3 years (respectively, 22.4% and 16.3%) after RRT. Thus, tumor recurrence and metastases occurred in 4.1% and 8.2% of cases during the first year after the start of RRT, reached a maximum in the 3rd year (22.4% and 16.3%, respectively), in the 5th decreased to 2.0% and 6.1%.

In the group of patients treated with RRT after laryngectomy, the number of patients with recurrence and metastasis was recorded within the first year after starting treatment (2.2% and 6.4%, respectively). At this time, the same number of metastases (2.2%) developed during 1-3 and 3-5 years, no recurrence was noted.

Thus, groups I and II were practically the same according to the above-mentioned parameters. However, the volume of treatment significantly affected the development of recurrence and metastases, as well as the survival rates of patients.

Table 1**Incidence rate of recurrence and metastases in RRT and LE+RRT groups**

Patient group and treatment method	Number of patients		Recurrence						Metastases						Total	
	absolute	%	Up to 1 year		1-3 years		3-5 years		Up to 1 year		1-3 years		3-5 years			
			absolute	%	absolute	%	absolute	%	absolute	%	absolute	%	absolute	%	absolute	%
I. RRT	49	100	2	4,1	11	22,4	1	2,0	4	8,2	8	16,3	3	6,1	29	59,1
II. LE +RRT	46	100	1	2,2	-	-	-	-	3	6,4	1	2,2	1	2,2	6	13

Thus, the combined treatment with LE significantly reduced the development of recurrence and metastases within 5 years - 4.5 times (from 59.1% to 13.0%); increased the 3 and 5-year survival rates of patients (71.7-67.3%, respectively) compared to remote gamma-therapy (RGT) alone (51.0-40.8%, respectively); reduced total mortality from 59.1% to 32.6%.

The results show that the laryngectomy + remote radiation therapy combined treatment method is superior to remote radiation therapy alone. However, the rehabilitation of patients with stage III laryngeal cancer who have lost an organ after LE is a very difficult and unsolved problem. For this reason, in most cases, patients absolutely refuse that surgical operation.

During chemo-radiotherapy in advanced laryngeal cancer, residual formation of larynx is often observed, and there is also a high chance of recurrence. In such cases, total laryngectomy is performed for the patients. However, in cases of total laryngectomy is performed after chemo-radiotherapy, complications are often observed in patients after surgery. In study, we analyzed the complications in preoperative radiation therapy and after total laryngectomy, especially the formation of pharyngocutaneous fistula (PCF). We found that the postoperative complications of 96 patients with stage III laryngeal cancer underwent total LE at the Department of Head and Neck Tumor of the National Center of Oncology were related to preoperative radiation therapy or performing neck dissection.

Patients were divided into two groups: Group I - 46 patients who received RRT+LE Group II - 50 patients who received LE+RRT (table 2).

Pharyngocutaneous fistula was more common after surgery in patients who received preoperative radiation therapy- 24 patient-38,5%, Surgical operation – closure of pharyngostomy was performed once in 5 of these patients and 2 times in 1 patient. These facts increase the patient's stay in the hospital, prolong nasogastric tube feeding, and will have a negative effect on the patient's psychological state and prolong the the patient's depression period. Fistula was observed in 5 patients –3,5% who received radiation treatment after total LE.

Table 2**The risk ofpharyngocutaneous fistula formation depending on RRT+LE and LE+RRT treatment methods**

Patient groups and treatment methods	Number of patients		PCF						PCF						Total	
	absolute	%	1 week						2 week				3 week		absolute	%
			absolute	%	absolute	%	absolute	%	absolute	%	absolute	%				
RRT+LE	46	100	2	4,1	6	5,2	1	2,0	4	8,2	8	9,3	3	9,7	24	38,5
LE+RRT	50	100	1	1,0	-	-	-	-	2	1,4	1	0,5	1	0,6	5	3,5

Only one patient underwent repeated surgery- closure of pharyngostomy. PCF was closed in 4 patients as a result of conservative treatment. Fistula opening was not associated with neck dissection. As the time from radiotherapy to total LE surgery decreased, the frequency of fistula formation and time to fistula closure increased significantly. There were no significant differences in hemoglobin and albumin in preoperative laboratory blood tests. But the number of lymphocytes was quite low in patients with pharyngocutaneous fistula. Thus, based on our observations, fistulas, relapses and metastases occur less often in cases that surgery (LE) followed by radiation therapy.

The results of PCT+RRT and LE+RRT+PCT treatments in patients with stage T3N0-1M0 laryngeal cancer.

In the study, the effectiveness of neoadjuvant and adjuvant chemotherapy in condition of radiation exposure in stage III laryngeal cancer was comparatively studied. This treatment was performed on groups III and IV that patients underwent combined treatment. 15 patients (11.7%) received 2 courses of neoadjuvant polychemotherapy (on day 1 cisplatin 80 mg/m² and on days 1-5 fluorouracil 750 mg/m², SD 3750-5000 mg + remote radiation therapy SSD 2 Gr) and 2 course adjuvant chemotherapy with the same scheme; Group IV consisting of 18 (14.0%) patients underwent: LE+ remote radiation therapy TSD 40 Gr + 2 courses of neoadjuvant intra-arterial polychemotherapy (taxotere 75 mg/m² and cisplatin 80 mg/m² on 1 day - courses were repeated every 21 days).

The number of men (80.0% and 83.3%, respectively) was almost 4 times more than the number of women (20.0% and 16.7%) in the PCT+RRT and LE+RRT+PCT (III and IV) groups. The majority of patients were in the age range of 51-70 years (66.6% and 61.1%). Thus, according to age and gender, the patients of both groups were practically same.

In terms of the characteristics of tumor development and localization in different areas of the larynx in both groups, there were more patients with exophytic tumors (60.0% and 55.5%, respectively). Most of them were glottic tumor, (73.3% and 66.7%). Therefore,

the studied groups were slightly different in terms of the these parameters.

In terms of tumor size, the majority of patients in both groups (53.3% and 55.6%, respectively) had tumors larger than 4 cm. Analysis of the prevalence of metastases revealed that the majority of group III and IV patients did not have metastases (T3N0M0): 86.7% and 88.9%, respectively. Regional lymph node metastases (T3N1M0) were noted in 2 (13.3%) patients of group III and 2 (11.1%) of group IV.

All patients with T3N1M0 in both groups underwent fascial-futular excision of soft tissues of neck in case of N1.

The results of the study showed that after the combined surgical treatment (LE+RRT+PCT) compared to the PCT+RRT group, there was a significant difference in the incidence rate and duration of the development of recurrence and metastases.

As shown in table 3, the incidence of recurrence and metastases was 27.7% in the LE+RRT+PCT group, and 66.6% in the PCT+RRT group ($P < 0.05$). At this time, more metastases developed after PCT+RRT 6 (39.9%) than relapses – 4 (26.7%). After the combined treatment of LE+RRT+PCT, the development of metastases occurred only in 1 (5.5%) case, and relapses developed in 4 (22.2%) patients. These results showed that the effectiveness of the combined treatment method of LE+RRT+PCT proposed by us is higher than that of PCT+RRT, with a 2.4-times reduction in the total number of relapses and metastases.

The analysis of the duration of recurrence and metastases showed that recurrence and metastases occurred more often within 1 year after PCT+RRT. Although relapses developed in only 4 (26.7%) patients within 1 year, it was not recorded in the later periods. Metastases were observed in 3 (20.0%) cases within 1 year, 2 (13.3%) within 1-3 years, and 1 (6.6%) within 3-5 years.

In patients receiving combined treatment of LE+PCT+RRT, recurrence was observed in only 4 (22.2%) cases up to 1 year, metastases developed in only 1 (5.5%) case within 1-3 years.

Table 3

Incidence rate and duration of recurrence and metastases in laryngeal cancer patients treated with PCT+RRT and LE+RRT+PCT methods

Patient groups and treatment methods	Number of patients		recurrences						metastases						Total	
	absolute	%	up to 1 year		1-3 years		3-5 years		up to 1 year		1-3 years		3-5 years			
			absolute	%	absolute	%	absolute	%	absolute	%	absolute	%	absolute	%	absolute	%
I.PCT+RRT	15	100	4	26,7	-	-	-	-	3	20,0	2	13,3	1	6,6	10	66,6
II.LE+RRT+PCT	18	100	4	22,2	-	-	-	-	-	-	1	5,5	-	-	5	27,7

The analysis of the incidence rate of recurrence and the development of metastases by years showed that in the first year, patients of group IV with the treatment method presented by us, compared to group III, had 4.5% less relapses and there were no metastases, during 1-3 years - there were no relapses and metastases were 2.4 times less, for 3-5 years - there were no relapses or metastases. Thus, the combined therapy with IAPCT (intra-arterial polychemotherapy) + LE method developed by us allows to reduce the development of relapses and metastases within 5 years after starting treatment, and in some cases - to prevent them. In comparison with remote radiation therapy, LE + RRT and polychemotherapy + remote radiation therapy, the results obtained from the LE + PCT + RRT treatment method showed a significant effectiveness in improving the treatment results of patients with stage III laryngeal cancer.

Survival indicators of patients with stage T3N0-1M0 laryngeal cancer depending on the treatment method.

At present, the most correct method of representing life expectancy of oncology patients is life tables. In some sources, this method is called statistical, dynamic or actuarial. If all patients die at the end of the observation, these life tables are exactly the same as life expectancy (the ratio of living patients to the total number of treated patients) calculated by the straight method.

We choose the interval method as a modification used in the calculation of life tables. In this method, we divide patients into several groups according to the interval accepted for the establishment of life tables, taking into account the patients who died, who are out of observation (in our study - according to year) in the period of observation.

According to our results, the 1-year cumulative life expectancy of laryngeal cancer patients after RRT was maximally high, that is, equal to 100%. However, in the next follow-up periods, the cumulative survival rate decreased suddenly ($P < 0.05$). Thus, the 2-year survival rate is decreased to $66.7 \pm 7.0\%$, 3-year - $40.6 \pm 7.0\%$, 4- and 5-year - $18 \pm 6.7\%$ and $18 \pm 0\%$ respectively. These figures showed that the 4- and 5-year survival rates of laryngeal cancer patients treated with conventional radiation therapy are significantly lower ($P < 0.05$) (table 4).

The survival indicators of the patients who underwent LE+RRT (group II) were significantly different from patients of group I. So, the 1-year cumulative survival rate of patients who underwent LE+RRT (group II) was lower than RRT group (I) - $87.7\pm 5.01\%$. Despite the fact that the 2-year survival rate of patients who underwent LE+RRT decreased to $81.7\pm 4.7\%$, this figure was significantly higher than the same survival rate of patients who received RRT ($66.7\pm 7.0\%$). The 3-year survival rate was $52.0\pm 9.6\%$, the 4-year survival rate was $52.0\pm 0\%$, and the 5-year survival rate was $26.0\pm 13.0\%$. These indicators were higher than in group I ($40.6\pm 7.0\%$, $18\pm 6.7\%$ and $18\pm 0\%$, respectively). Thus, despite the fact that the 1-year survival indicators of patients who underwent LE+RRT were lower compared to patients who received only RRT, the 4- and 5-year survival indicators were significantly higher.

Analysis of survival indicators of PCT+RRT (group III) patients resulted in higher than previous groups. Thus, the 1-year cumulative survival rate in patients underwent PCT+RRT reached a maximum of 100% (as in the patient group receiving RRT). The 2-year survival rate of patients who underwent PCT+RRT was $84.7\pm 9.9\%$, and was higher than the indicators of the RRT ($66.7\pm 7.0\%$) and LE+RRT ($81.7\pm 4.7\%$) groups. The 3-year survival rate in PCT+RRT group decreased to $50.8\pm 15.1\%$ (approximately the same as in the RRT+LE group - $52.0\pm 9.6\%$), but was higher than RRT group ($40.6\pm 7.0\%$). However, the 4-year survival rate decreased to $30.4\pm 15.6\%$ in PCT+RRT group (as in the RRT group - $18.0\pm 6.7\%$), which was lower than LE+RRT group ($52.0\pm 0\%$). The 5-year survival rate was $30.4\pm 0\%$ in this group. This indicator was higher than the indicators of the groups of RRT ($18.0\pm 0\%$) and LE+RRT ($26.0\pm 13.0\%$) (table 4).

Thus, the results showed that the 2- and 5-year survival rates of patients underwent PCT+RRT (84.7% and 30.4% , respectively) were significantly higher than RRT group (66.7% and 18.0% , respectively), was relatively higher than LE+RRT group (81.7% and 26.0% , respectively) ($P < 0.05$).

Table 4

3- and 5-year cumulative survival rates of patients with stage III laryngeal cancer depending on treatment method

Patient groups and treatment methods	Number of patients		cumulative survival rates, M \pm t, %	
	absolute	%	3-year	5-year
I. RRT	49	100	40,6 \pm 7,0%	18,0 \pm 0%
II. LE+RRT	46	100	52,0 \pm 9,6%	26,0 \pm 13,0%
III. PCT+RRT	15	100	50,8 \pm 15,1%	30,4 \pm 0%
IV. LE+RRT+PCT	18	100	66,3 \pm 12,6%	66,3 \pm 0%

The analysis of survival rates of IV group (LE+RRT+PCT) patients showed that this treatment method is superior to other methods. Thus, cumulative 1-year survival rate of this patient group was maximal, as in the group of RRT and PCT+RRT -100%, but it differed from RRT+LE group (87.7 \pm 5.1%). The 2-year survival rate of patients in LE+RRT+PCT group was 86.7 \pm 8.7%, and this indicator was higher compared to other groups (RRT-66.7 \pm 7.0%, LE+RRT-81.7 \pm 4,7% and PCT+RRT-84,7 \pm 9,9%). The 3-year survival rate of LE+RRT+PCT group was 66.3 \pm 12.6%, which was higher than the indicators of RRT (40.6 \pm 7.0%), LE+RRT (52.0 \pm 9, 6%) and PCT+RRT groups (50.8 \pm 15.1%). The 4- and 5-year survival rates in the LE + PCT + RRT group were 66.3 \pm 0% and were significantly higher than other groups (RRT, 18.0 \pm 6.7% and 18.0 \pm 0%, respectively; LE +RRT-52.0 \pm 0% and 26.0 \pm 13.0%; PCT+RRT 30.4 \pm 15.6% and 30.4 \pm 0%).

Thus, in comparing the 3- and 5-year survival rates of patients received the new treatment method with the results of other patient groups, statistically significant differences were found (P<0.05). The results showed that the 2-, 3-, 4- and 5-year survival indicators of the patients were higher in LE+RRT+PCT group.

Thus, as a result of the research, it was possible to evaluate the effectiveness of laryngectomy, polychemotherapy under different radiation conditions in the treatment of T3N0-1M0 laryngeal cancer, and to analyze the probable survival indicators of the patients after various combined treatment methods. A new combined treatment

method allowed to improve the treatment results of patients with T3N0-1M0 laryngeal cancer.

CONCLUSIONS

1. In patients with T3N0-1M0 laryngeal cancer, radiation therapy after laryngectomy reduces both the formation of pharyngocutaneous fistula within the first weeks and the development of recurrence and metastases within 5 years by 4.5 times (from 59.1% to 13.0%)[1,2].
2. Compared with single remote radiation therapy (51.0% and 40.8%, respectively), laryngectomy increased the 3- and 5-year survival rate of patients with T3N0-1M0 laryngeal cancer (71.7% and 67%,3 respectively) and reduced overall mortality from 59.1% to 32.6%[4,6].
3. The treatment method consisting of laryngectomy + remote radiation therapy + systemic polychemotherapy was able to reduce the development of recurrence and metastases by 2.4 times (from 66.6% to 27.7%) within 5 years, and to increase the 3- and 5-year survival rates and to reduce total mortality by 1.8 times (from 40.0% to 22.2%) [6,7].
4. Complex treatment of patients with stage T3N0-1M0 laryngeal cancer with a radical program also increases the 3- and 5-year survival rates, the effectiveness of treatment by 20% compared to other methods [7,8].

PRACTICAL RECOMMENDATIONS

1. Laryngectomy should remain the main combined treatment method in the treatment of T3N0-1M0 laryngeal cancer.
2. The combined use of radiation therapy and chemotherapy allows achieving long-term remission, but does not improve the 3- and 5-year survival indicators of patients.
3. The combined treatment of laryngectomy+remote radiation therapy+polychemotherapy developed by us significantly reduces the development of pharyngocutaneous fistula, recurrence and metas-

tases, and improves the life expectancy of most patients compared to other treatment methods. For this reason, the use of this treatment method can be the preferred method of treating patients with III laryngeal cancer.

4. Involving the mass media to broadcast information on the prevention, as well as early detection of HPV among the population of the Republic of Azerbaijan within the framework of the "National fight against cancer" program.

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LIST OF ABBREVIATIONS AND TERMS

PCT– polychemotherapy

CT– computed tomography

LC – laryngeal cancer

Gr – Gray

RRT– remote radiation therapy

LE–laryngectomy

MRI– magnetic resonance imaging

USM – ultrasound examination

PCF – pharyngocutaneous fistula

SSD – single source dose

TSD – total source dose

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