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Research Article

A Novel Approach of IORT: Efficacy and Safety of Intraoperative Radiation Therapy for Locally Advanced Laryngocarcinoma

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Abstract

Background: Intraoperative Radiation Therapy (IORT), as a short- range irradiation mode, has been increasingly used in surgery in head and neck cancer. IORT can achieve and improve local control by directly irradiating the tumor bed after surgery. However, there are few clinical reports on the efficacy and safety of IORT in the treatment of Locally Advanced Laryngocarcinoma (LAL).

Methods: This is a prospective clinical study in which a total of 63 LAL patients were selected and received IORT (DT 8-15 Gy) during radical surgery. In order to record postoperative complications and adverse reactions after radiotherapy, a regular follow-up was conducted after completion of IORT. The Local Control (LC) and 2nd year survival rate were analyzed.

Results: In this study 63 patients, 2-year LC rate was 93.1% and 1-year LC rate was 98.2%. After surgery combined with IORT, serious postoperative complications occurred, including pharyngeal fistula in 1 patient (1. 6 %) and wound infection in 3 patients (4.8%).

Conclusion: IORT can improve the LC rate in LAL patients and is a safe and effective treatment method.

Keywords: Locally advanced laryngocarcinoma; Intraoperative radiation therapy; Local control; Efficacy and safety; External beam radiation therapy

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INTRODUCTION

Laryngocarcinoma as one of the common malignant tumors of head and neck, has seriously threatened the health of Chinese residents. According to global cancer statistics, the number of new patients with laryngocarcinoma in the world in 2020, has exceeded 1,80,000, and the number of deaths among laryngocarcinoma patients was close to 100,000 [1]. A newly published study in China also shows that, although the standardized morbidity and standardized mortality of laryngocarcinoma in Chinese residents showed a downward trend from 2005 to 2016 [2], with the continuous growth of aging population, the mortality of laryngocarcinoma began to rise slowly, and we still face great challenges in diagnosis and treatment of this disease. For locally advanced laryngeal cancer, the local recurrence rate remains 19%-40% after radical surgery with postoperative radiotherapy alone or with concurrent chemoradiotherapy inpatients with unfavorable

prognostic factors [3-5]. The high rate of recurrence will seriously affect the quality of life and survival time of patients. Therefore, we are still exploring effective methods to improve the LC rate clinically. IORT can improve the LC rate by directly irradiating the tumor bed with high-dose low- energy X-rays [6]. In recent years, as a short-range irradiation mode, IORT has played an important role in treatment of breast cancer, brain glioma and other malignant tumors, and has been increasingly used in the surgery in head and neck cancer.

At present, the clinical treatment for patients with LAL mainly include radical surgery combined with postoperative external irradiation, and IORT is still rarely used. Based on this, we evaluate local control and acute toxicity of IORT as a tumor bed boost for locally advanced laryngeal cancer in this prospective phase 2 trial.

MATERIALS AND METHODS

Study design

In this study, PASS software 2021 version was used to calculate the sample size. In this single-arm, single-center clinical trial, we included eligible patients into the study, followed up their adverse reactions and complications 1, 3, 6, 9, 12, 18 and 24 months after receiving IORT therapy, and assessed the safety of IORT. The results of regular postoperative imaging and laryngoscopy were recorded, and the efficacy of IORT was analyzed and determined.

Subjects

The subjects in this study were all LAL patients diagnosed histopathologically in Tianjin First Central Hospital who received radical surgery (total laryngectomy/hemilaryngectomy) combined with IORT and received local external irradiation within 6 weeks after surgery. The subjects were enrolled from 1 January, 2019 to 30 September, 2021 and had signed the informed consent form.

Inclusion criteria: 1) Subjects at age of ≥ 18 years; 2) Subjects who were pathologically diagnosed as locally advanced laryngeal squamous cell carcinoma with staging of T2N1-3/T3N0-3/T4N0-3;

3) Subjects who had indication of radical surgery (total laryngectomy / hemilaryngectomy) and agreed to receive surgery; 4) Subjects with estimated survival time of ≥ 3 months.

Exclusion criteria: 1) Subjects who received EBRT before surgery;

2) Subjects with distant metastasis; 3) Subjects who had previous history of other malignant tumors; 4) Subjects whose postoperative tumor bed was not suitable for IORT; 5) Subjects who had contraindications of follow-up CT/MRI examination; 6) Subjects who refused to accept follow-up or loss of follow-up; 7) Subjects with previous serious diseases of other systems; 8) Subjects who were pregnant or planned to be pregnant; 9) Subjects who participated in other clinical trials.

Treatment method

IORT treatment method: All the patients enrolled were treated with the INTRABEAM system for IORT during radical surgery (total laryngectomy/hemilaryngectomy). The IORT system was calibrated and verified in terms of the probe of the IORT control system, dynamic deviation of the electron beam, isotropy and dose delivery, etc. Then the simulated dose distribution of IORT was verified using GMV Radiance ver 3.0. After tumor resection, a treatment probe of the appropriate diameter (1.5 cm to 5.0 cm, with increment of 0.5 cm) was selected based on the exposed surgical area volume. The treatment probe was connected to the probe of the mobile 50KV X-ray source intraoperative radiotherapy equipment (INTRABEAM, Carl Zeiss), and the radiotherapy site was jointly determined by the otolaryngology surgeon and radiation oncologist together. The choice of applicator type is directly related to the operation method. The flat applicator was used in total laryngectomy and the spherical applicator was used in hemilaryngectomy to fit the tumor bed. In addition, the edge of the skin incision was evaginated to avoid excessive radiation exposure. After preparation, the tumor bed area with high risk of tumor recurrence was subjected to a single high-dose irradiation according to the treatment plan. The prescribed dose of 100% volume X-ray was 8-15Gy, and the radiotherapy time was 7-20 minutes. The surgery was completed by suturing the wound after intraoperative radiotherapy. For the specific condition as shown in Figure 1.

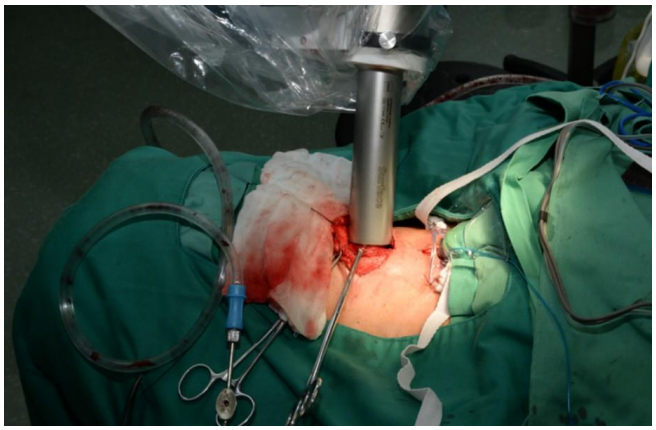

Figure 1: IORT Treatment process.

Postoperative external irradiation treatment method: All patients were required to begin EBRT within 4-6 weeks after IORT, and the median of time is 5 weeks (35 days). The range of target area delineated is as follows: GTVtb includes tumor bed, surgical bed, and the whole area invaded by the primary tumor, none of them subject to radiotherapy

boost; if the metastatic lymph nodes invaded into extrapulmonary sites, muscles or blood vessels, the primary region of the metastatic lymph node should be delineated as GTVnd-tb. Clinical Target Volume (CTV) includes GTVtb, GTVnd-tb, other areas of larynx, hypopharynx, tongue vallecula epiglottitis, paraglottic space, preepiglottic space and the whole thyroid cartilage, sub-area of dissected lymph nodes and high- risk lymph node drainage area. For supraglottic laryngeal carcinoma, CTV should include lymphatic drainage areas of upper and middle neck (zones Ⅱ and Ⅲ). If the upper and middle cervical lymph nodes are positive, CTV should include the whole bilateral neck. Tracheostomy fistula should also be included in the target area sketching in cases of subglottic region invasion, emergency tracheostomy performed before surgery, cervical soft tissue invasion, positive tracheal incision margin or insufficient safety boundary, and surgical incision marks passing through the fistula. The Planning Target Volume (PTV) was generated by expanding the CTV by 0.3 cm isotropically in all dimensions. All the patients received EBRT at a total therapeutic dose of 54-60Gy to PTV within 6 weeks after surgery, 5 times per week, 1.8-2 Gy per time, 30 times in total.

Subject follow-up

- The subjects should receive regular follow-up within 2 years after IORT. One month after surgery, the subjects started to receive follow-up every 3 months in the first year, and every 6 months in the second year.
- The following contents were recorded during follow-up: Postoperative complications (occurrence, duration and outcome); adverse reactions after treatment (classified according to RTOG for acute radiation injury); regularly reexamine CT, MRI, laryngoscope and other relevant examination results; and whether there are other anti-tumor treatments.

Study endpoints

Primary endpoint: Safety issues after receiving IORT and local control after receiving IORT. The safety indicators were assessed, including postoperative local tissue necrosis and fibrosis; wound healing time; wound infection; pharyngeal fistula; radiation-induced pain; skin and mucous injury; chondronecrosis; salivary gland injury; loss of taste; dyspnea, etc.

Secondary endpoint: 2-year survival rate.

Statistical analysis

PASS software 2022 version was used to calculate the sample size, with a statistical power of 80%. SPSS software 27.0 version (IBM, USA) was used for statistical analysis. The counting data is expressed in percentage (%). χ^2 test was adopted for comparison between the two groups, which showed statistical significance ($p<0.05$). Kapalan- Meier method and log rank test were adopted to analyze and determine local control and survival.

RESULTS

Baseline characteristics

A total of 63 LAL patients, 59 males and 4 females, aged 40 years to 81 years, with a median age of 61 years, were enrolled in the study and regularly followed up from January, 2019 to September, 2021. All the 63 LAL patients received radical surgery (hemilaryngectomy/total laryngectomy), IORT (DT 8-15Gy) and EBRT (DT 54-60Gy). Among them, 14 patients had supraglottic LAL, 44 patients had glottic LAL and 5 patients had subglottic LAL; 10 patients showed high differentiation

and 44 patients showed moderate differentiation and 9 patients showed low differentiation of laryngeal squamous cell carcinoma; 3 patients were in T2N1-2 stage, 40 patients in T3N0-2 stage and 20 patients in T4N0-2 stage; 48 patients received total laryngectomy and 15 patients received hemilaryngectomy; 16 patients were lymph node-positive and 1 patient developed vascular tumor thrombus after surgery. For the specific baseline characteristics as shown in Table 1.

Univariate analysis of recurrence and clinical pathological factors

63 patients were included in this study. The last follow-up time was 30 April, 2022 and the median follow-up time was 20 months (7 months-39 months). Among these patients, 3 patients experienced cancer recurrence, and 60 patients did not. In this study, cancer recurrences were not related with smoking, alcohol drinking, laryngocarcinoma staging, tumor differentiation, preoperative staging, IORT dose and other clinicopathological factors, postoperative pathological lymph nodes. Positive postoperative pathological vascular tumor thrombus associated with recurrence-free survival time (HR 21.099; 95% CI, 1.879 to 236.976; P 0.013). The detailed results are shown in Table 2.

Short-term acute toxic and adverse reactions (primary endpoint)

The last follow-up time of the study was 30 April, 2022 and the median follow-up time was 20 months (7 months-39 months). The complications and adverse reactions in the first and third month of follow-up were defined as short-term acute toxic and adverse reactions, as shown in Table 3.

Baseline data	N=63	(%)
Gender		
Male	59	-93.70%
Female	4	-6.30%
Age		
< 60 years old	27	-42.90%
≥ 60 years old	36	-57.10%
Smoking		
Yes	57	-90.50%
No	6	-9.50%
Alcohol drinking		
Yes	34	-54.00%
No	29	-46.00%
Laryngocarcinoma typing		
Supraglottic type	14	-22.20%
Glottic type	44	-69.80%
Subglottic type	5	-8.00%
Tumor differentiation		
High differentiation	10	-15.90%
Moderate differentiation	44	-69.80%
Low differentiation	9	-14.30%
Preoperative t staging		
T2	3	-4.80%
T3	40	-63.50%
T4	20	-31.70%
Preoperative n staging		
N0	50	-79.40%

N1	11	-17.50%
N2	2	(3. 1%)
Surgical method		
Hemilaryngectomy	15	-23.80%
Total laryngectomy	48	-76.20%
Postoperative pathological lymph nodes		
Positive	16	-25.40%
Negative	47	-74.60%
Postoperative pathological vascular tumor thrombus		
Positive	1	-1.60%
Negative	62	-98.40%
Surgical incisal margin condition		
Positive	0	
Negative	63	-100%
IORT dose		
8-10gy	15	-23.80%
12-15gy	48	-76.20%

Table 1: Baseline characteristics of patients enrolled.

Factor	Bivariate analysis			Multivariate analysis		
	P	HR	95% CI	P	HR	95% CI
Age ≥ *vs*<60 years	0.263	0.274	0.028 to 2.641			
Smoking (yes *vs* no)	0.214	0.215	0.019 to 2.430			
Alcohol drinking (yes *vs* no)	0.469	0.412	0.037 to 4.549			
Tumor ferentiation (high *vs* moderate *vs* low)				0.038	7.335	1.112 to 48.380
Hemilaryngectomy *vs* total	0.549	0.035	0.00 to 2054.48			
(Supraglottic type *vs* glottic *vs* subglottic)				0.74	0.738	0.122 to 4.444
Preoperative (t2 *vs* t3 *vs* t4)				0.596	0.58	0.078 to 4.340
Preoperative (n0 *vs* n1 *vs* n2)				0.751	1.375	0.193 to 9.804
Postoperative pathological lymph nodes (positive *vs* negative)	0.244	3.215	0.451 to 22.912			
Postoperative pathological vascular tumor thrombus (positive *vs* negative)	0.013	21.099	1.879 to 236.976			

Table 2: Bivariate/Multivariate analysis result of recurrence and clinicopathological factors.

Complications and adverse reactions	N	(%)
Local tissue necrosis and fibrosis after surgery	0	
Delayed wound healing	3	-4.80%
Wound infection	3	-4.80 %
Pharyngeal fistula	1	-1.60%
Radiation-induced pain		
Rtog grade 1 or 2	12	-19.40%
Rtog grade 3 or 4	1	-1.60%
Skin and mucous injury		
Rtog grade 1 or 2	3	-4.80%

Rtog grade 3 or 4	0	
Chondronecrosis	0	
Salivary gland injury		
Rtog grade 1 or 2	4	-6.40%
Rtog grade 3 or 4	0	
Taste dysfunction	4	-6.40%
Dyspnea (rtog grade 4)	2	-1.60%

Table 2: Bivariate/Multivariate analysis result of recurrence and clinicopathological factors.

Local control (primary endpoint)

In this study, 3 of 63 LAL patients had local recurrence symptoms, with a 2nd year local control rate of 93.1% and a 1st year local control rate of 98.2%.

2nd year survival rate of patients (secondary endpoint)

Three of the 63 patients enrolled died, with a 2nd year survival rate of 98.4%, for the specific conditions.

DISCUSSION

This is single-arm, single-center clinical trial, and the study utilized a bit of favorable group with the majority (79.4%) having node negative disease. In fact, such patients are less likely to recurrence. Therefore, our study has some limitations. Most notably, our study is the first prospective trial to our knowledge to demonstrate the local control effect of intraoperative radiotherapy as a tumor bed boost for locally advanced laryngeal cancer. Among the 63 LAL patients included in this study, 3 patients developed local recurrence around trachea (2 patients) or in thickened soft tissue in the postoperative bed (1 patient). The study reported a 2nd year local control rate of 93.1% and a 1st year local control rate of 98.2%, and only 1 patient developed a serious complication (pharyngeal fistula), indicating that the treatment has high safety. A long-term study with follow-up period of 10.8 years provided the results of a nonsurgical treatment strategy to preserve the larynx in 520 LAL patients. The study found that 3rd year local control rates of RT combined with induction chemotherapy or chemotherapy or RT alone are 58.2%, 71.1%, 53.6% respectively [3]. In the RTOG 9501 phase Ⅲ trial with a median follow-up period of 9.4 years, the local-regional failure rates were 28.8% *vs* 22.3% for patients treated by RT *vs* RT+CT, respectively. In patients with microscopically involved resection margins and/or extracapsular extension, local-regional failure occurred in 33.1% *vs* 21.0%, respectively [4]. Another postoperative study compared high dose radiotherapy with radiochemotherapy in patients presenting with locally advanced head and neck cancers. According to the results of follow-up, 5th year local-regional recurrence rate was significantly lower in radiochemotherapy group than in the radiotherapy alone group (21.0% *vs* 33.1%) [5]. Relevant studies found that recurrence rate of LAL after standard treatment is still high, so improvement of the local control of patients has a positive effect on prognosis of patients, which requires development and application of intraoperative radiotherapy technology.

IORT technology has been applied in clinical practice since 1960s and has gradually developed up to now.

The IORT combined with surgery has the following advantages [7]

- It can reduce the chance of residual disease at the surgical site by eliminating the tumor lesions under the microscope.
- It can prevent tumor recurrence because it requires no Surgery-Radiation Interval (SRI) in which tumor cells can proliferate. Therefore, the tissues under surgical intervention have rich vascularization and aerobic metabolism, and are more sensitive to the effects of radiation, so the radiobiological effects of a single high-dose irradiation can be maximized.

After resection of tumor tissue, brachytherapy with low- energy X-rays can directly apply total or almost total therapeutic dose to the fully exposed tumor bed in the surgical area, avoiding radiation damage to the surrounding normal tissues, and reducing the incidence of radiotherapy complications [8]. At present, intraoperative radiotherapy is mostly used in treatment of breast cancer, pancreatic cancer, rectal cancer, soft tissue sarcoma and other tumors. Relevant studies have confirmed that adding intraoperative radiotherapy to the standard treatment can improve the local tumor

control rate and prolong the survival time of patients [9] and IORT is safe and reliable. No evidence of increasing postoperative complications has been found [10].

An analysis of the efficacy and safety of IORT for head and neck cancers showed that [11], the application of IORT combined with EBRT in head and neck cancers can improve local control, and effectively prolong the survival time and the safety has been preliminarily confirmed. A related meta-analysis for a clinical trial of IORT on 21 head and neck malignant tumors found that, the 2-year LC rate of patients without residual IORT after surgery was 90%, and IORT had a good safety as an adjuvant treatment [12]. However, another related study shows that [13], when applying IORT to head and neck tumors, in order to avoid radiation damage to the surrounding normal tissues, the maximum single dose of IORT is required to be controlled within 20 Gy, but a low dose of IORT cannot eliminate the residual lesions in the tumor bed. Therefore, how to balance the benefits of efficacy and the risks of adverse reactions and determine the optimal radiation dose is also one of the most important works in future. After 63 patients in this study received surgery combined with IORT, 3 patients had postoperative infection (4.8%) and 1 patient had pharyngeal fistula (1.6%); only 3.2% (2/63) had RTOG grade 3 adverse reactions after combined external irradiation and no RTOG grade 4 adverse reactions were found; In addition, 4 patients with taste impairment recovered within 3 months after EBRT. It can be confirmed that patients with IORT combined with EBRT have a low incidence of serious toxic and adverse reactions in short term, and this treatment mode is safe and reliable. In addition, the 2nd year LC rate and the 1st year LC rate in this study was 93.1% and 98.2%, respectively, both higher than the results of other relevant studies, confirming that the application of IORT resulted in an improved efficacy. The study site will continue to conduct relevant studies with larger sample size and longer follow-up period to obtain further clinical benefit.

LIMITATIONS

The main limitations are that our study was done at a single institution and does not offer a randomized comparison with conventional postoperative radiotherapy. However, intraoperative radiotherapy is rarely used in head and neck cancer and its toxicity is not well understood. We adopted a single-arm design in this study, and we will further conduct a phase 3 randomized controlled study to address the limitations of this data. Another notable limitation of our study is the short follow-up. However, larger series of patients with longer follow-up show that the median time to local recurrence for locally advanced laryngeal cancer occur by 2 years after treatment. Finally, for patients with T3 and T4, radiotherapy is the first choice in most centers, but our MDT team will still recommend treatment strategies for patients from the perspective of achieving the maximum local control rate, using adjuvant radiotherapy after radical surgery. After surgical and pathological confirmation, most patients with locally advanced laryngeal cancer enrolled in this study have negative pathological lymph nodes after surgery, which is a group of patients with good overall prognosis. However, for 95% of the whole group of patients with T3 and T4, the local control rate selected in this study is still a key indicator to evaluate the success of local treatment.

CONCLUSION

In summary, our trial proved that the addition of intraoperative

radiotherapy as a tumor bed boost to postoperative radiotherapy provided local therapeutic benefit to patients with locally advanced laryngeal cancer. Our data support the safety of the combined therapy. Additional investigation is warranted to determine the role of intraoperative radiotherapy in the local treatment of locally advanced laryngeal cancer. The integration of IORT into treatment protocols could potentially redefine therapeutic strategies and enhance the quality of life for patients with LAL.

DECLARATIONS

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Authors Contributions: Wu Q and Liu Q analyzed the data and edited the manuscript. Wang Y reviewed the protocol and prepared the manuscript. Zheng Y and Wang X treated patients and prepared the manuscript. Peng X reviewed the protocol and edited the manuscript. X Wang collected patients' information. Wei X collected patients' information and prepared the manuscript. Zhang S helped with conception of study and edited the manuscript. Yang Y and Li L treated patients and prepared the manuscript. Yang Y and Li L collected patients' information.

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Availability of data and materials: The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

Ethics approval and consent to participate: The study was approved by the Tianjin First Central Hospital Ethics Committee. The ethical approval number is 2018N026YY. Written informed consent will be obtained from all participants.

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