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Original Article

Role of CCRT In T3n0 Squamous Cell Carcinoma Larynx, Pros Vs Cons

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ABSTRACT

Objective: To assess the use and efficacy of Concurrent Chemoradiotherapy for a T3N0 Laryngeal Cancer as a Laryngeal Function Preservation modality.

Study Design: Prospective Study design

Place and Duration of Study: CMH Rawalpindi, Pakistan from January 2022-January 2023.

Methodology: The sample size was n=24, having TPF-CCRT from January 2022 to January 2023 was chosen by using a purposive sampling technique. Individuals were having abnormalities of T3 glottis without vocal cord fixation. Along with MRI, the pretreatment evaluation also comprised clinical, endoscopy, and ultrasound examinations with or without fine needle pick cytology samples. Moreover, F-fluoro-2-deoxy-D-glucose positron emitting tomography was used for whole-body CT scanning. The UICC TNM grading method was used to grade the tumors as grade 15.

Results: Twelve out of 24 patients had grade 1 tumor (50%), eight had grade 2 tumors (25%), and four had grade 3 tumors (25%). There had been complete resolution among 17 (70%) of patients, while the disease remains persistent disease in 7 (30%) patients. 95% of patients found with good speech and breathing. 95% of patient organs remain preserved. All 24 patients received CCRT. Four individuals (20%) without tumor regression received surgery following 40 Gy of RT. Others received RT with a 66 Gy median total dose.

Conclusion: The study found that effective cancer control is possible with CCRT, and its effects are manageable in 70% of patients with tolerable toxicity. However, in 30% of cases, it fails, requiring salvage laryngectomy. However, the search for a viable strategy with tolerable toxicity and functional status is underway.

Keywords: Adjunctive chemotherapy, Concurrent, Laryngeal, Radiotherapy, Squamous cell carcinoma, T3NO,

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INTRODUCTION

The most prevalent laryngeal carcinoma is squamous cell carcinoma (SCC), which develops in the glottis.[1] Medical scanning techniques like computerized tomography (CT) and functional MRI (fMR) imaging, in conjunction with a medical assessment, have been necessary for T-staging because the Organisation recommended the 6th update of the TNM grading method for Global Cancer Prevention and Control in 2022.[2] With such a 5-year localized controls (LC) incidence of 50%–60%, radiotherapy (RT) by itself is acknowledged as a conventional approach for the disease. Nonetheless, its therapeutic success is insufficient.[3,4] Concurrent chemoradiotherapy (CCRT) has indeed been employed to enhance therapeutic outcomes and is advised in the most recent recommendations. There are, nevertheless, few data on the effectiveness of CCRT in treating this illness.[5]

Concurrent chemoradiotherapy (CCRT) was established as a standard of care for LP after the RTOG study verified its value.[6] Surprisingly, some studies noticed a fall in laryngeal cancer individuals' overall survival throughout the later 1990s, with a tendency to increase CCRT spread after the establishment of CCRT's involvement in LP (and a gradual reduction in surgeries). The RTOG study.[7] showed improved laryngeal survival with concurrent CRT, which contributed to improving the idea of laryngeal retention. These findings have led to a progressive acceptance of radiation (RT)-based laryngeal sparing methods in the treatment of advanced or metastatic laryngeal carcinoma. These strategies.[8] have been suggested to be psychological processes for chosen individuals who have low-volume T3a malignancy or even less. Yet, this shift in approach has sparked a lot of debate concerning the long-term outcomes and relevance to a diverse patient group. Nevertheless, these database evaluations also discovered stable or slight increases in five-year relative life expectancies among individuals with severe laryngeal cancer and declining mortality rates among individuals with small laryngeal tumors (T1N0 and T3N0).[9]

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T3 illness is laryngeal carcinomas that are restricted to the glottic larynx with vocal cord fixation, penetration of the thyroid cartilage's internal cortex, and extension through into the paraglottic fat compartment.[10] Individuals with locally metastatic cancer who are enrolled in controlled clinical studies for therapy frequently have T3 glottic laryngeal carcinomas, with 60% to 78% appearing without nodal illness. The assessment of T3N0 individuals with relation to care and the effect of CCRT, along with overall survival, is necessary given the incidence of individuals with progressed laryngeal malignancies. Therefore, the effectiveness (pros and cons) of CCRT for T3N0 squamous cell carcinoma (SCC) without vocal cord fixation was assessed in the current study.

METHODOLOGY

A prospective Study design was chosen to evaluate the role of CCRT in squamous cell carcinoma. The study was conducted in CMH Hospital Rawalpindi from January 2021 to January 2023, ERB no 400. Sample size was calculated using sample size calculator. Confidence interval was kept 95 with 5% margin of error. Population proportion was kept 50% and total population was entered as 25. Keeping these values under consideration, the calculator gave me a sample size selection as 24 that was then become a basis of data collection for study.

Inclusion Criteria: The hospital's research management ethics office approved this prospective investigation. Individuals of either gender with ages ranging from 25-60 presented in the medical department with abnormalities proven T3 glottic SCC without vocal cord fixation were included in this study. Those who met the requirements for TPF-CCRT.

Exclusion Criteria: Individuals having comorbidities including diabetes, heart disease, and pregnant females were eliminated from the study. Individuals with extensive hypopharyngeal cancer that coexisted with patients were also excluded from the study.

Twenty-four of them had TPF-CCRT treatment at our institution. One patient got RT alone after declining chemotherapy. All individuals provided their prior written consent before their medical data was used in any investigations.The institutional head and neck tumor committee, which consists of a radiologist, otolaryngologist, and radiation oncology, completed the clinical grading.

In addition to MR scanning with or without gadolinium-based contrast media, the pretreatment evaluation also comprised clinical, endoscopy, and ultrasound examinations with or without fine needle pick cytology samples. Moreover, F-fluoro-2-deoxy-D-glucose positron emitting tomography was used for whole-body CT scanning. According to the 6th to 8th edition of the UICC TNM grading method, the tumors were graded.[15]

Individuals had to be between the age of 25 - 60 years, have a life survival expectancy of 2 months at least, a performance status of 0-2, and have enough haematological, hepatic, and renal functions (bilirubin concentration of 1.4mg/dl, aspartate aminotransferase level of 2 upper labile, Hb level >9.0g/dl, platelets levels>100,000/mm3, creatinine <1.3mg/dl, clearance of creatinine >55ml/min, total bilirubin concentration of 1.4mg/dl, aspartate aminotransferase level ≤2× upper limit of normal (ULN), and alanine aminotransferase concentration of <2 x ULN along with no complications. One or two TPF cycles are made up of concurrent chemotherapy.

From day 1, the individuals received an hour-long intravenous injection of docetaxel (50 mg). On days 1–6, continual intravenous administration of 5-FU (600 mg/m2/day) was started over one hour following the end of the docetaxel infusion.

With the help of 4-MV longitudinal accelerators, CRT was given. The patients received lateral fields of opposing local radiation therapy. Without elective nodal irradiation, the size of the field was generally 7X7-8X8 cm. RT was administered using a 2 Gy portion once per day. The head and neck malignancy board carried out an interim evaluation to examine the tumor regression based on endoscopic inspection and MR imaging results following the administration of 40 Gy and one round of chemotherapy.

In the prior time frame, total laryngectomy (n=2) and laryngeal preservation (n=2) were performed on four individuals (20%) who were deemed to have no tumor regression. The final 20 patients had RT at a total radical dosage of 64–70 Gy (median, 66 Gy).

The follow-specific ups are provided elsewhere. Essentially, individuals were checked on every month for the first year following the end of their therapy, every two months for the next year, and then every four months after that. At every follow-up appointment, physical and endoscopic tests were conducted. Furthermore, within two months of the end of the therapy and then every four months after

that, or as medically necessary, post-treatment MR, CT, and ultrasound were done.

The demographics method was used to determine the percentages of LC, laryngeal retention, and overall survival from the time of treatment beginning. According to the earlier studies16, the individuals who required operation and had a satisfactory pathological improvement to the therapy were terminated at the time of surgery for the calculation of LC.

The SPSS version 25 program was used to do numerical calculations. Descriptive statistical analysis was done to find out the frequency distribution of respondents and group the historical grading to tumors Age was represented in mean and standard deviation while frequency was determined for other variables.

RESULTS

The study included patients with a mean age of 55±27.50 years. The majority of patients 88% were male (n=21) while 12% of patients were female (n = 3)

Stage three (3) illness affected every single patient. In 23 cases, the tumor was fixed and limited to the larynx, and in the remaining two patients, the pyriform fossa was affected. These parameters are displayed in Table I.

n=2 (8.3%) of the four patients who had undergone surgery following the administration of 40 Gy had pathologically detectable residual cancer, while the other three had a total histological response to the radiation therapy. No patient experienced local aspiration and died from pneumonia throughout the follow-up phase following a course of therapy, perhaps as a result of the tumor recurrence. n=2 (8.3%) people passed away from other ailments. Neither of the patients showed signs of local or widespread collapse. According to histology, n=2 (50%) of the 24 patients had grade 1 tumors, eight had grade 2 tumors, and four had grade 3 tumors (see Table II).

After a few weeks of therapy, an MRI scan taken post-treatment revealed complete disease remission in 17 patients, but the disease persisted in 7 others who required a salvage laryngectomy. Table III shows the therapeutic efficacy of CCRT.

Twenty-three patients were able to comprehend the speech, whereas one patient had limited or no understanding. No individuals required a permanent tracheostomy due to aspiration and breathing problems. Because of their ongoing dysphagia, none of the patients needed a persistent gastrostomy; one of them belonged to all those who also had tracheostomies. Twenty-three organs were preserved in total (95%), but only one was kept with satisfactory function (5%). Table IV illustrates the retention of organs and function.

Table I: Demographic Characteristics of The Patient (n=24)

Study Parameters	
Age in years (Mean±Sd)	55±27.50 (range 25 years to 60 years)
Gender frequency	
Male Female	21(88%) 3(12%)
Disease extension(Mean±Sd) Stage 3 (Fixed to the larynx) Stage 3 (involves pyriform)	23±29.20 2±5.50

Table-II: Histological Grading of Tumor (n=24)

Tumor	**Histology**	**Frequency (%)**
Grade 1	SCC well differentiated	12(50%)
Grade 2	SCC moderately differentiated	8(33%)
Grade 3	SCC poorly differentiated	4(16%)

Table III: Treatment Response to CCRT (n=24)

Treatment	**Result**
Complete resolution	17(70%)
Persistent disease	7(30%)

Table IV: Function and Preservation of an Organ (n=24)

Function	**Organs preserved**	**Results**
Speech	Understand Poor	23(95%) 1(5%)
Breathing	Normal Need tracheostomy	24(100%) -
Swallow	Able to swallow	23(95%)
Organ preservation	Organ preserved Satisfactory function	23(95%) 1(5%)

DISCUSSION

Intending to cure 24 individuals with T3N0 laryngeal squamous cell carcinoma, we assessed the efficacy of surgical and CCRT-based treatments. At two years, the overall survival rate for all treatment modalities was almost 55%. Although Kaplan-Meier analysis did not reveal any changes in lifespan, multivariate analysis revealed that daily divided CCRT was linked with poorer survival than rapid RT. This result corroborates regard for trying to treat sufferers who choose RT-based laryngeal preservation strategies11 but are ineligible for concurrent CRT with expedited RT fractionation regimens and is coherent with the results of randomized clinical experiment

information going to compare RT timetables that include five fractions per week vs. speeded up 6 fractions per week in laryngeal malignancy.

The Cancer Institute Dataset was used by study[12] to evaluate 52,816 patients treated between 1985 and 2007; they found a rise in the use of radiation treatment administered with or without chemotherapy from 8% to 44%. From 43% to 34%, a primary complete laryngectomy was performed. Whole laryngectomy, CCRT, and RT each had 4-year overall survival rates of 52%, 47%, and 37%, respectively. Utilizing SEER data, Pulte *et al*.[13] observed gains in head and neck cancer sufferers' life expectancies over the latter part of the 20th century compared to people living with laryngeal cancer.

The Cancer Institute Dataset Research in this field in the USA revealed that this was also confirmed for a current series of cases identified between 2004 and 201214. There were 385 ICT cases, 1596 CCRT cases, and a maximum of 1558 SRT cases. CCRT was discovered to be linked with worse OS compared to RT and ICT (HR, 1.24 P<0.01) after controlling for variables. These statements caused a stir. For instance, poor patient choice for the LP approach may result in a worse chance of survival for individuals who have locally progressed laryngeal cancer. Until RCT results may be applied to standard clinical practice, some critical elements must nevertheless be understood.[15]

More aggressive treatment approaches have been adopted for T3N0 glottic malignancy without vocal cord fixation as a result of studies[11,16] of CCRT alone with traditional fractionation. The effectiveness of CCRT for [16]individuals with T3 glottic cancer was assessed by study[13].15(94%) of the 16patients had N0 pathology, while 1(6%) had N1 ailment. Fifty-two percent of eight individuals had vocal cord fixation. With cisplatin-based treatment, an average RT dosage of 70 Gy (range=63-71.5 Gy) was administered with a once-daily portion of 2-2.17 Gy. The laryngectomy-free survival, overall survival, and five-year LC rates were 86%, 82%, and 88%, correspondingly. Our survey's LC, LP, and effectiveness rates were deemed to be equal to or higher compared to the earlier publications.

Our research findings show that CCRT is 70% effective, although in 30% of individuals, it fails, and patients need a salvage laryngectomy. The benefit of CCRT is that it aids the patient in maintaining both their voice and their organs. The CCRT patients did not experience aspirations-related problems. Yet, the data show that when CCRT fails, a complicated laryngectomy is required.

Hematologic abnormalities and oral thrush are the main acute toxicity of TPF-CRT, as per research 17 administered TPF-CCRT to 23nasopharyngeal cancer patients. This study found that mucositis and Grade 2-3 neutropenia occurred in 11(41%) and 15(68%), correspondingly, of the participants. In terms of hematologic malignancies, our findings were comparable to theirs. However, compared to their findings, our findings demonstrated reduced mucositis, most likely as a result of the exclusion of ENI. The toxicity we came across was generally acceptable.

According to the groundbreaking publishing by the Veterans Affairs Laryngeal Carcinoma Research Group18, concurrent chemotherapy and radiation treatment had effectiveness that was comparable to surgical intervention and radiotherapy, and they also had the additional advantage of preserving the larynx in two-thirds of the patients they treated. Nonetheless, irrespective of the organ's functional capacity, organ preservation in this research resembled that of an "organ in situ."

Moreover, a study17 presented a randomized experiment wherein the concurrent chemoradiation treatment in one group of individuals and radiation therapy solely in another group of individuals were compared to induction chemotherapy immediately by irradiation. The experiment demonstrated that CCRT provided the best results for participants who could tolerate chemotherapy. Nevertheless, patients receiving other treatments did not have a different overall survival rate. Compared to the VA research, the documentation of laryngeal functions (swallowing, speaking, and breathing) was present in this trial, which is required for a useful evaluation of the results.

Regional failure following the end of therapy was rare. We earlier reviewed [18,19] 63cases treated with RT with or without chemotherapy to examine the recurrent trend of graded or restaged T3N0 illness without vocal cord fixation (4). Of the 63 patients, 41(65%) got CCRT with low-dose or TPF-chemotherapy, while 22(33%) received RT alone. After receiving 40 Gy, 11 patients (17%) had total laryngectomy or LP surgery since the tumor did not regress. A cumulative RT dose of 65–73 Gy was given to the remainder of 53 patients (median, 66 Gy). Recurrence occurred in 18 individuals (28%) of whom were classified as failure mode exclusively.

Radiation therapy, either with or without chemotherapy, was formerly one of the primary treatment options for T3 glottic cancer, and just a few individuals underwent it[20]. As a result, five patients went into treatment at the beginning of our series after receiving 40 Gy, although it was later determined that far more than fifty percent of the individuals had a total clinical reaction to the 40 Gy of RT and one round of TPF. A comprehensive recovery can be achieved with radical CCRT, although if patients don't see tumor regression at the moment of interim evaluation, given the outstanding LC in our trial.

Our research has some drawbacks. Firstly, there were just a small number of participants in this prospective analysis. Secondly, following the administration of 40 Gy and one cycle of chemotherapeutic, few patients underwent surgery. Surgery's potential for bias could have an impact on our findings.

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LIMITATION OF STUDY

Limited Sample size and data from only one tertiary care center were our limitations during our study.

CONCLUSION

In summary, CCRT offered excellent cancer control for T3N0 glottic carcinoma without vocal cord fixation, with tolerable toxicity. Our research concluded that CCRT is 70% effective, although in 30% of individuals, it fails, and patients need a salvage laryngectomy. The overall performance is noticeably higher when functional organ preservation is taken into account, but the general view is strong enough to support the argument for non-surgical organ retention. The search for a reasonable strategy with tolerable toxicity and a respectable functional status with sufficient speaking, respiratory, and feeding is still underway. A viable strategy recommended for the condition is extensive local therapy with CCRT.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AK: & NR: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

FM: & KZ: Data acquisition, data analysis, approval of the final version to be published.

MSA: & MA: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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