Oncologic and Functional Outcomes in Advanced Laryngeal and Hypopharyngeal Cancer Treated with Concurrent Chemoradiation versus Primary Surgery Followed by Adjuvant Treatment

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Objective: *To compare oncologic outcomes in advanced laryngeal and hypopharyngeal cancer (LHC) patients who received either concurrent chemoradiation (CRT) or primary surgery followed by adjuvant treatment and to examine functional outcomes in the patients treated with CRT.*

Material and Method: *The clinicopathological data of 136 patients, diagnosed as stage III or IV LHC, were retrospectively reviewed. The eligible patients were classified into two groups based on their primary treatment, CRT group and group of surgery followed by the adjuvant treatment. Oncologic outcomes were evaluated and compared at five years. Functional outcomes were recorded as tracheostomy and/or feeding tube dependency.*

Results: *Five-year overall survival rates were 66.9% for the primary surgery group and 34.8% for the CRT group (p = 0.004). Five-year disease-specific survival rates for the same two groups were 66.9% and 39.9%, respectively (p = 0.03). The three-year laryngectomy-free survival rate in the CRT group was 71.9%. At three months post-CRT, 62.3% of patients depended on tracheostomy and/or a feeding tube.*

Conclusion: *The primary surgery followed by adjunctive treatment among the advanced LHC cases had significantly better oncologic outcomes. Nevertheless, CRT group had a high survival rate with a preserved larynx, but with relatively inferior functional outcomes.*

Keywords: *Laryngeal cancer, Hypopharyngeal cancer, Concurrent chemoradiation, Surgery*

J Med Assoc Thai 2013; 96 (9): 1164-8
Full text. e-Journal: *http://jmat.mat.or.th*

Laryngeal and hypopharyngeal cancer (LHC) are the common cancers of the head and neck. In 2008, worldwide estimated age-standardized rates (ASRs) of LHC were 2 to 2.3 per 100,000 population, and around 177,000 LHC deaths yearly worldwide[1]. Over 50% of LHC patients have locally advanced disease at the time of diagnosis. For decades now, the standard treatment of advanced stage LHC has been radical surgery. The laryngectomy provides satisfactory disease control, although it inevitably leaves several unpleasant aftermaths such as handicap, social isolation, job loss, and depression[2,3].

To improve the quality of life and lessen morbidity from mutilating surgery of LHC patients, chemoradiation has become an increasingly common therapy over the last decade, with a view to attempting to preserve the larynx, both physically and functionally. In the beginning, induction chemotherapy was introduced in advanced LHC in an attempt to achieve uncompromising disease control and be effective in preserving the larynx[4,5]. Since that beginning, advances in chemotherapy and radiation therapy have improved locoregional control and reduced the rate of laryngectomy by administrating chemotherapy and radiation concurrently[6]. However, long-term side effects following concurrent chemoradiation (CRT) such as speech or swallowing dysfunction have been observed in several studies[7,8]. One study found that such delayed-appearance complications related to functional outcomes occurred in up to 20% of patients undergoing chemoradiation for locally advanced head and neck carcinomas[9].

Currently CRT is the common organ preservation regimen when feasible in LHC, with upfront laryngectomy still used as radical treatment in advanced LHC. The aims of the present study were to

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compare oncologic outcomes in advanced LHC patients who received either CRT or primary surgery followed by adjuvant treatment, and to examine functional outcomes in the patients treated with CRT.

Material and Method

With ethical approval by the institutional review board, the present study was retrospectively conducted. The clinicopathological data of 136 patients who were diagnosed as advanced stage of LHC, between January 2006 and December 2011, were reviewed.

At time of receiving treatment all patients were defined as stage III or IV, AJCC 2002 TNM staging, by physical examination and imaging documentation. The eligible patients were classified into two groups based on the primary treatment plan, CRT or primary surgery followed by adjuvant treatment. The decision on which treatment to give was based on the multidisciplinary tumor board recommendation, which was in turn made on the basis of a combination of advanced stage LHC treatment and the patient's preference, as well as the patient's T classification, medical condition, performance status, desire to preserve the larynx and risks of general anesthesia.

The CRT group received platinum based chemotherapy concurrently with external beam radiation. The given chemotherapy regimens were intravenous 100 mg/m^2 of cisplatin or carboplatin at a dose of area under the concentration-time curve (AUC) 4 to 6 on day-1, -22, and -43, and carboplatin at a dose of AUC 2 weekly up to 7 cycles. Conventional technique radiotherapy was delivered in single daily fractions of 2.0 Gy, to a total dose of 66 to 70 Gy. Post-treatment evaluation was based on a physical examination and/or imaging after the complete CRT course, with salvage surgery considered if the tumor response was less than complete response.

The primary surgery group underwent the laryngectomy or larygopharyngectomy, varying from partial to total laryngeal and hypopharyngeal removal, ground on tumor extension and the patient's clinical status. Adjuvant treatment, the radiation or chemoradiation, was delivered postoperatively according to the pathological results. Patients with adverse pathological features such as positive pathological margin or extracapsular extension of the lymph nodes also received platinum based chemotherapy concurrent with the postoperative radiotherapy. The adjuvant radiation dosage to the target area was at least 50 Gy.

During the follow-up period, careful physical examinations, blood tests, and radiological investigation were periodically performed, monitoring the signs of recurring disease. If recurrent disease was found, the appropriate salvage treatment was offered to deem curable.

Clinical follow-up data with at least three months post-treatment until death was included in the study, with recurrences, overall survival (OS), and disease specific survival (DSS) noted. The study period of each patient was from the date of clinical diagnosis until the date of their last examination. Laryngectomy-free survival (LFS), tracheostomy and feeding tube dependency were noted in the CRT group. Descriptive statistics were used to describe frequency and percentage or median and range. Kaplan-Meier curves were used to describe the survival probability in relation to the study variables. The probabilities of survival at 5-year with a 95% confidence interval were calculated using the standard Kaplan-Meier estimate. Statistical test p-values for differences in survival curves were obtained by the method described by Harrington and Fleming[10]. All statistical methods were performed using R statistical software version 2.13.0[11].

Results

Patient population

The characteristics of all patients are listed in Table 1. The majority of patients were male (97.8%) and the median age of the overall group was 62.5 years (range, 51 to 71 years). All patients were re-staged according to the AJCC 2002 staging system, with stage distribution of stage III: 57 (41.9%), and stage IV: 79 (58.1%). Eligible patients received primary surgery followed by adjuvant treatment (n = 75), and CRT (n = 61).

Overall and disease-specific survival

The median follow-up time in the study was 15.19 months. At the time of analysis, 37 patients had died, 33 of disease and 4 of other causes. The 5-year OS and DSS rates of the LHC were 52.1% and 55%. The primary surgery/chemoradiation group, the 5-year of OS was statistically significant of 66.9%/34.8% (p = 0.0043), as well as 5-year DSS of 66.9%/39/9% (p = 0.0293), as demonstrate in Fig. 1 and 2.

The 5-year DSS of hypopharyngeal cancer population, primary surgery/chemotherapy group, was 81.7%/37.1%, with significant difference (p = 0.0492), while of laryngeal cancer group was 55.3%/53.2%, without significance (p = 0.0621).

Table 1. Characteristics of study subjects by primary treatment group (n = 136)

	Surgery No. (%) n = 75	Chemoradiation No. (%) n = 61	p-value
Gender			1.000
Male	71 (94.7)	58 (95.1)	
Female	4 (5.3)	3 (4.9)	
Median age (range)	65 (56, 71)	60 (51, 69)	0.058
Differentiation			0.071
Well	22 (29.3)	11 (18.0)	
Moderate	30 (40.0)	27 (44.3)	
Poor	18 (24.0)	11 (18.0)	
Unknown	5 (6.7)	12 (19.7)	
Primary tumor			<0.001*
Larynx	52 (69.3)	21 (34.4)	
Hypopharynx	23 (30.7)	40 (65.6)	
T stage			0.004*
T1	5 (6.7)	2 (3.3)	
T2	3 (4.0)	15 (24.6)	
T3	45 (60.0)	28 (45.9)	
T4	22 (29.3)	16 (26.2)	
N stage			<0.001*
N0	39 (52.0)	13 (21.3)	
N1	15 (20.0)	18 (29.5)	
N2	21 (28.0)	25 (41.0)	
N3	0 (0)	5 (8.2)	
AJCC staging			0.470
III	34 (45.3)	23 (37.7)	
IV	41 (54.7)	38 (62.3)	
Total	75	61	

* Statistical significance, p<0.05

Organ preservation

There were 54 patients scheduled for chemotherapy every three weeks, of whom 34 (63%) received three cycles and 17 (31.5%) received two cycles. Seven patients were scheduled for chemotherapy weekly, of whom four received six cycles and three received four cycles. Only three subjects underwent laryngectomy due to disease recurrence, or non-functionality of the remaining larynx. At 3-year post-treatment, the LFS of preserved larynx group was 71.9%.

Tumor response and salvage surgery

For the CRT group, 42 of 61 (68.8%) patients achieved complete response. Of 12 of partial response and seven of progressive disease, the management included palliative therapy in majority of nearly two-third, and the rest comprised of salvage surgery, and second line chemotherapy.

Dependency on tracheostomy and/or feeding tube

According to the CRT group, at 3-month post-treatment the dependency composed of tracheostomy and a feeding tube of 15 in 61 (24.6%) cases, a feeding tube of 12 (19.7%) cases, and tracheostomy of 10 cases (18.0%).

Discussion

In the present study, the 5-year OS (52.1%) and DSS (55%) of LHC patients are comparable to the result of previous studies, which reported the 5-year survival rate of advanced stage LHC from 24.8 to 73%[12,13].

In comparison between treatment modalities, significantly better 5-year OS and DSS rates from primary surgery followed by adjuvant treatment were shown in the hypopharyngeal cancer subgroup, although this is at variance with an earlier retrospective study which revealed no significant difference in the 5-year OS and DSS between surgery and CRT[12].

In laryngeal cancer, a recent retrospective study examining the oncologic outcomes in advanced laryngeal cancer treated with either primary surgery or CRT reported that at 2-year, OS was 84% following surgery and 64% with CRT, and DSS was 84% with surgery and 80% following CRT, with no statistically significant differences[14]. In the present study, the 5-year OS and DSS rates between primary surgery followed by adjuvant treatment and CRT were also not significantly different.

A number of factors would influence the treatment outcomes in a retrospective study of surgery versus CRT, including the high possibility of physician selection bias; i.e. chemoradiation among complicated cases rather than surgery.

At present, CRT provides the rates of laryngeal preservation, from 44.8 to 88% in various studies[6,12-15]. The 3-year LFS rate was 71.9% in the present study, which is comparable to the previous studies. These rates can be expected to improve as better methods are found to counteract the potential toxicities related to CRT, which can cause treatment to be interrupted before the complete course.

A dependency on either tracheostomy or a gastrostomy tube for speech or swallowing is considered as indicators of CRT consequences. The present study found the same occurrence of some unsatisfactory functional outcomes of the larynx as previous studies. In LHC patients undergoing chemoradiation, the reported rates of gastrostomy dependence varied from 8 to 41% at 1 year and from 4 to 22% at 2-year[8,13,16-21],

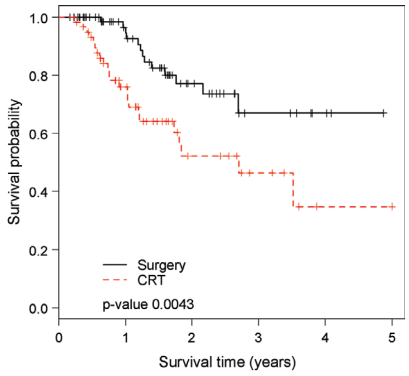

Fig. 1 Overall survival (OS) of the advanced stage LHC cases, comparison between primary surgery followed by adjuvant treatment and concurrent chemoradiation.

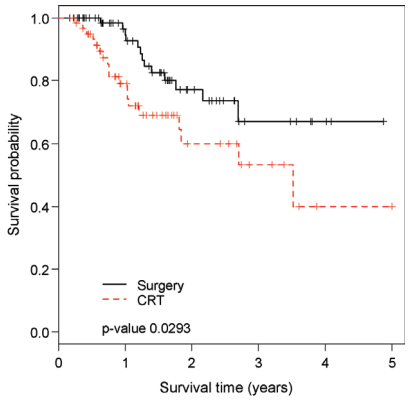

Fig. 2 Disease specific survival (DSS) of the advanced stage LHC cases, comparison between primary surgery followed by adjuvant treatment and concurrent chemoradiation.

and the rate of tracheostomy dependence was reported at 8.5%[13]. Some suggestions have been made to try to reduce this feeding tube dependency, such as not installing a feeding tube upfront and encouraging patients to use their swallowing mechanisms during treatment for the longest period of time. However, many patients suffering from cancer have poor oral intake prior to treatment and need to have their nutritional status improved with a feeding tube. To minimize feeding tube dependency, proper timing of the feeding tube installation needs to be clarified.

In conclusion, the primary surgery followed by adjunctive treatment among the advanced LHC cases had significantly better oncologic outcomes than CRT. Nevertheless, the CRT group had a high survival rate with a preserved larynx, but with relatively inferior functional outcomes.

Potential conflicts of interest

None.

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ผลการรักษาของมะเร็งกล่องเสียงและคอหอยส่วนล่างระยะลุกลามด้วยเคมีบำบัดร่วมกับรังสีรักษาเปรียบเทียบกับการผ่าตัดตามด้วยการรักษาเสริม

กิตติ จันทรพัฒนา

วัตถุประสงค์: *เพื่อเปรียบเทียบผลการรักษามะเร็งกล่องเสียงและคอหอยส่วนล่างระยะลุกลามระหว่างเคมีบำบัดร่วมกับรังสีรักษากับการผ่าตัดตามด้วยการรักษาเสริม และเพื่อตรวจสอบผลที่ได้รับการทำหน้าที่ในผู้ป่วยเคมีบำบัดร่วมกับรังสีรักษา*

วัสดุและวิธีการ: *ทบทวนข้อมูลคลินิกพยาธิวิทยาของผู้ป่วยมะเร็งกล่องเสียงและคอหอยส่วนล่างระยะ 3 และ 4 ย้อนหลังจำนวน 136 ราย แบ่งผู้ป่วยเป็น 2 กลุ่มตามการรักษาปฐมภูมิ กลุ่มเคมีบำบัดร่วมกับรังสีรักษา และกลุ่มการผ่าตัดตามด้วยการรักษาเสริม ประเมินและเปรียบผลที่ได้รับด้านมะเร็งวิทยาเมื่อสิ้น 5 ปี ผลที่ได้รับด้านหน้าที่การทำงานด้วยการพึ่งพาการเจาะคอ และ/หรือ การให้อาหารทางสายยาง*

ผลการศึกษา: *อัตราการรอดชีวิตโดยรวมที่ 5 ปี ของกลุ่มผ่าตัดปฐมภูมิ และเคมีบำบัดร่วมกับรังสีรักษา เท่ากับร้อยละ 66.9 และ 34.8 ตามลำดับ (p = 0.004) อัตราการรอดชีวิตเฉพาะโรคที่ 5 ปี ของกลุ่มผ่าตัด และเคมีบำบัดร่วมกับรังสีรักษา เท่ากับร้อยละ 66.9 และ 39.9 ตามลำดับ (p = 0.03) อัตราการรอดชีวิตโดยไม่ตัดกล่องเสียงออกที่ 3 ปี ในกลุ่มเคมีบำบัดร่วมกับรังสีรักษา เท่ากับร้อยละ 71.9 ที่ 3 ปี หลังเคมีบำบัดร่วมกับรังสีรักษาการพึ่งพาการเจาะคอ และ/หรือ การให้อาหารทางสายยาง เท่ากับร้อยละ 62.3*

สรุป: *กลุ่มผ่าตัดปฐมภูมิตามด้วยการรักษาเสริม ในผู้ป่วยมะเร็งกล่องเสียงและคอหอยส่วนล่างระยะลุกลาม ให้ผลที่ได้รับด้านมะเร็งวิทยาดีกว่าเคมีบำบัดร่วมกับรังสีรักษาอย่างมีนัยสำคัญ กระนั้นก็ตาม กลุ่มเคมีบำบัดร่วมกับรังสีรักษามีอัตรารอดชีวิตสูงกว่ามากด้วยการสงวนกล่องเสียง แต่ผลที่ได้รับด้านหน้าที่การทำงานต่ำโดยสัมพัทธ์*