



Three therapeutic regimens based on induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck: a single center experience

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Background: This study aimed to compare three different therapeutic models based on regional control and the outcome of locally advanced squamous cell carcinoma of the head and neck (SCCHN) after induction chemotherapy (ICT).

Methods: One hundred and twenty patients with locally advanced SCCHN were retrospectively reviewed and divided into three groups. Patients in Group A received induction chemotherapy + concurrent chemoradiotherapy (ICT + CCRT). Patients in Group B received induction chemotherapy + radical surgery + adjuvant radiotherapy with or without chemotherapy (ICT + Surgery + RT/CRT). Patients in Group C received induction chemotherapy + planned neck dissection + concurrent chemoradiotherapy (ICT + PND + CCRT). The clinicopathological characteristics, locoregional recurrence (LR), distant metastasis (DM), and overall survival (OS) were compared among them.

Results: The median follow-up time was 20 months. In Group A, Group B and Group C, the 3-year OS was 69.7%, 72.9%, and 65.5% respectively. The LR rate was 35.1%, 26.2%, and 42.9%, respectively. The DM rate was 10.5%, 31.0%, and 9.5%, respectively. There were no significant differences in OS and LR among three groups. The DM in Group B was significantly higher than that in Group A ($P < 0.05$), and was probably higher than that in Group C ($P = 0.06$).

Conclusions: Locally advanced SCCHN has a poor prognosis, and the first treatment is critical. Individualized therapeutic regimen based on the response of ICT could be an ideal solution. As cervical metastatic lymph nodes are less sensitive to ICT than primary tumors, PND before radiation therapy might improve the regional control and throat function preservation. A multidisciplinary team (MDT) collaboration is important throughout the treatment process.

Keywords: Squamous cell carcinoma; induction chemotherapy (ICT); concurrent chemoradiotherapy (CCRT); planned neck dissection (PND); multidisciplinary team (MDT)

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is one of the most common malignant tumors in the head and

neck, accounting for nearly 5% of adult's newly diagnosed neoplasms, and it includes oral cavity, oropharyngeal, hypopharyngeal, laryngeal carcinomas and so on, depending on the primary lesions. As its special anatomical structure,

head and neck tumors cover almost all functions related to pronunciation, speech, breathing, chewing, swallowing and etc. Patients with early-stage SCCHN (stage I–II) usually have favorable outcomes after radical surgery and/or radiotherapy (RT) (1). Nevertheless, the majority of patients present with locally advanced lesions or metastatic cervical lymph nodes (stage III–IV) at diagnosis. A combination of surgery, RT and chemotherapy determined by a multidisciplinary team (MDT) has been recommended as a standard treatment for locally advanced SCCHN (1).

The initial treatment of locally advanced SCCHN is still controversial. It is very important that the physiological function and the quality of life should be preserved as much as possible while the tumor has been well controlled. The tumor foci, clinical staging, pathological subtype, changes on appearance and function, probable complications, patient's socio-economic status should be considered systematically. Concurrent chemoradiotherapy (CCRT) is becoming the preferred treatment for advanced SCCHN while possesses bigger advantages in preserving organ function. However, the Chinese population has poorer tolerance to the toxicity and side effects of CCRT. Although surgery, a traditional and classical treatment, might not be the preferred choice, it is still an important therapeutic strategy, especially for those who relapsed after initial chemoradiotherapy (CRT). Induction chemotherapy (ICT), as a part of comprehensive treatments, has got much attention in recent years because it not only increases throat preservation, but also reduces distant metastasis (DM) (2–4). ICT is generally not used to treat SCCHN patients independently but to screen patients before surgery or RT. The response degree can to some extent judge the sensitivity of RT and the overall efficiency.

Through searching for clinical practice and previous studies, we found that the sensitivity of cervical metastatic lymph nodes to ICT and CCRT was significantly lower than that of the primary foci. Cervical lymph node progression was one of the main causes of failure in the treatment of locally advanced SCCHN. Therefore, we recommended neck dissection (ND) before CCRT for such patients whose primary tumor was significantly reduced, but lymph nodes were not.

It could be more flexible to choose following treatment strategy based on the response of ICT. The present study was specifically targeted on the patients who were initially treated with ICT. One hundred and twenty patients with stage III–IV SCCHN were retrospectively reviewed, the survival outcomes and locoregional control were compared among these patients who received three different ICT based treatments.

Methods

Patients

From June 2013 to May 2017, there were totally 2,247 patients diagnosed with SCCHN and treated in our hospital. Eventually, 120 well-documented patients were screened out. These patients were defined as locally advanced SCCHN without DM (stage III, IVA, and IVB) according to the American Joint Committee of Cancer (AJCC) staging system (7th edition), and received initial ICT treatment. Primary lesions affected oral cavity, oropharynx, hypopharynx or larynx. In the final analysis, 120 patients were divided into three groups according to the therapeutic strategies (Table 1). This study had been approved by the Ethics Committee of our Hospital [zjzlyy Medical Ethics Approval Document (2015)-01-21].

Treatments

All patients received two courses of ICT previously. Two weeks after the second cycle, the response to ICT was estimated by imaging examination including CT and/or MRI. Patients were then divided into three different groups according to the effects of ICT. Patients in Group A (both primary tumor and lymph nodes were significantly reduced) received concurrent chemoradiotherapy (ICT + CCRT), patients in Group B (both primary tumor and lymph nodes were not reduced significantly) received radical surgery + adjuvant radiotherapy with or without chemotherapy (ICT + Surgery + RT/CRT), and patients in Group C (primary tumor was significantly reduced, but lymph nodes were not) received planned neck dissection + concurrent chemoradiotherapy (ICT + PND + CCRT) (See Figure 1).

ICT regimens were determined by the physicians in a MDT. PF (cisplatin and 5-fluorouracil), TP (docetaxel and cisplatin), and TPF (docetaxel, cisplatin and 5-fluorouracil) regimens were chosen based on patient's age, performance status, primary lesion, and differentiation of tumor. The therapeutic efficacy was evaluated after two courses of ICT according to RECIST 1.1 criteria (typical cases were shown as Figures 2–4).

Radical surgery included radical resection of the primary tumor and simultaneous ND. Modified ND was applicable for N1–N2 patients, while radical ND for N3 patients.

Dose of radical RT was 66–72 Gy, while adjuvant RT was 60–66 Gy determined by radiologists. All patients received intensity-modulated radiation therapy (IMRT). Cisplatin was used during CCRT as a classic regimen, while carboplatin acted as an alternative if patients were intolerant to cisplatin.

Table 1 Clinicopathological characteristics of 120 patients with locally advanced SCCHN

Characteristic	Total	No. of patients (%)		
		Group A (ICT + CCRT)	Group B (ICT + Surgery + RT/CRT)	Group C (ICT + PND + CCRT)
N	120	57	42	21
Gender				
Male	115	53 (93.0%)	41 (97.6%)	21 (100%)
Female	5	4 (7.0%)	1 (2.4%)	0
Age (mean ± SD)	56.9±7.6	57.5±8.1	56.1±7.0	57.2±7.2
Primary tumor				
Oral cavity	3	0	3 (7.1%)	0
Oropharynx	41	21 (36.8%)	12 (28.6%)	8 (38.1%)
Hypopharynx	67	33 (57.9%)	22 (52.4%)	12 (57.1%)
Larynx	9	3 (5.3%)	5 (11.9%)	1 (4.8%)
TNM stage				
Stage III	11	6 (10.5%)	4 (9.5%)	1 (4.8%)
Stage IVA	107	49 (86.0%)	38 (90.5%)	20 (95.2%)
Stage IVB	2	2 (3.5%)	0	0
Tumor differentiation				
High differentiated	60	31 (54.4%)	19 (45.2%)	10 (47.6%)
High-moderate differentiated	6	4 (7.0%)	1 (2.4%)	1 (4.8%)
Moderate differentiated	21	7 (12.3%)	10 (23.8%)	4 (19.0%)
Moderate-poorly differentiated	9	4 (7.0%)	4 (9.5%)	1 (4.8%)
Poorly differentiated	20	8 (14.0%)	7 (16.7%)	5 (23.8%)
Undifferentiated	4	3 (5.3%)	1 (2.4%)	0
ICT regimens				
PF	32	15 (26.3%)	12 (28.6%)	5 (23.8%)
TP	34	19 (33.3%)	11 (26.2%)	4 (19.0%)
TPF	54	23 (40.4%)	19 (45.2%)	12 (57.2%)

Patients in Group A received induction chemotherapy + concurrent chemoradiotherapy, patients in Group B received induction chemotherapy + radical surgery + adjuvant radiotherapy with or without chemotherapy, patients in Group C received induction chemotherapy + planned neck dissection + concurrent chemoradiotherapy. TNM stage was determined according to the 7th edition of American Joint Committee of Cancer (AJCC) staging system. ICT regimens: PF, cisplatin and 5-fluorouracil; TP, docetaxel and cisplatin; TPF, docetaxel, cisplatin and 5-fluorouracil.

Follow-up

After completion of treatments, all patients were followed up once every 3 months in the first 2 years, and thereafter once every 6 months in the following years. The follow-up periods were calculated from the date of completion

of primary treatment to death or the last follow-up time. During the observation process, physical examination, laboratory examination, and imaging examination (including ultrasonography, endoscopy, CT or MRI) were routinely performed. If patients were diagnosed with recurrence or metastasis, further treatments such as

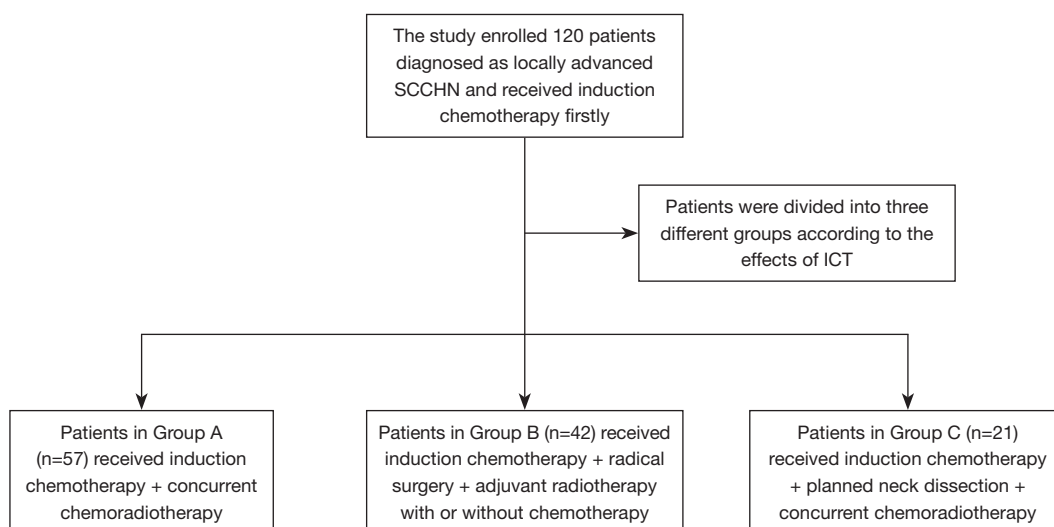


Figure 1 Flowchart of patients' grouping and treatments. ICT, induction chemotherapy.

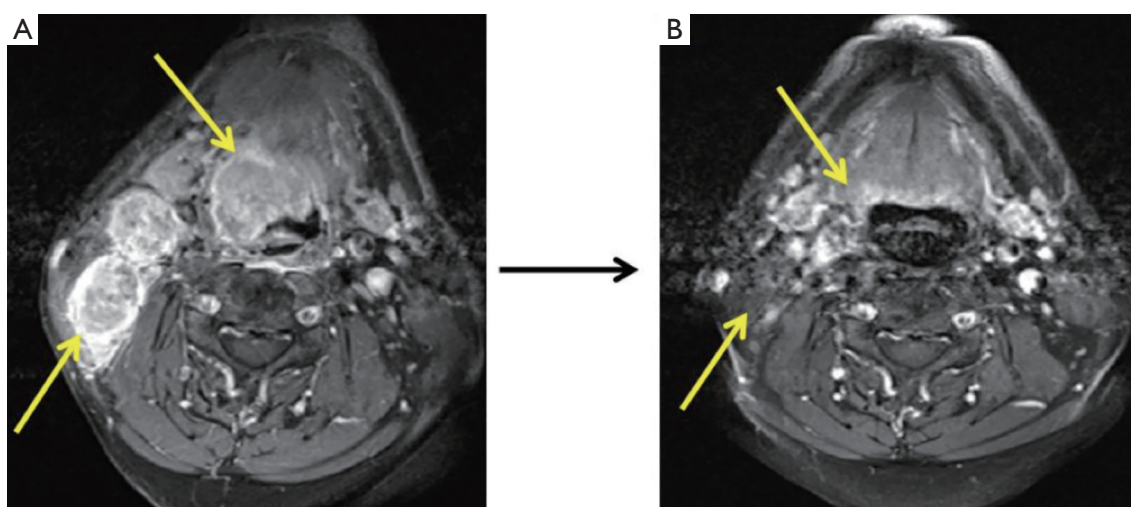


Figure 2 Typical case 1: before therapy, MRI image showed the tumor of right tongue root and the metastatic lymph node in right neck (A, upper yellow arrow showed the primary tumor, lower yellow arrow showed the metastatic lymph node); after 2 courses of ICT, MRI image showed both primary tumor and metastatic lymph node approached CR (B, upper yellow arrow showed the primary tumor, lower yellow arrow showed the metastatic lymph node). Case 1 received ICT + CCRT.

salvage surgery, palliative RT, palliative chemotherapy, targeted therapy, or best supportive care were employed individually.

Statistical analysis

The main endpoint was overall survival (OS, calculated

from the date of diagnosis to death or the last follow-up time). The secondary endpoints included locoregional recurrence (LR) and DM. Statistical analysis were performed with SPSS version 20.0 for Windows (IBM, Armonk, USA). Kaplan-Meier curves and Log rank test were used to describe OS. Chi-square test was used to compare the LR and DM. A value of $P < 0.05$ was considered

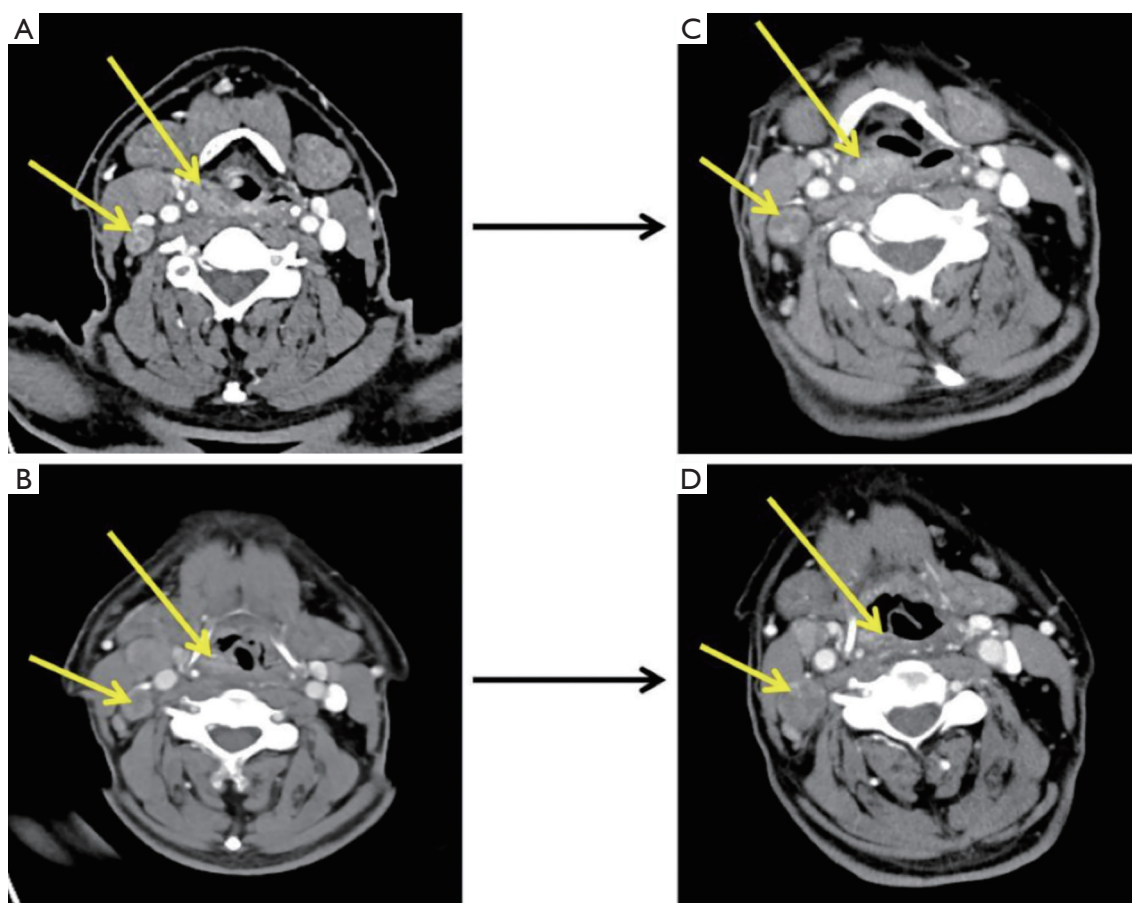


Figure 3 Typical case 2: before therapy, CT scan showed the tumor of right hypopharynx and the metastatic lymph node in right neck (A,B, upper yellow arrow showed the primary tumor, lower yellow arrow showed the metastatic lymph node); after 2 courses of ICT, CT scan showed the primary tumor maintained SD, while the metastatic lymph node reached to PD (C,D, upper yellow arrow showed the primary tumor, lower yellow arrow showed the metastatic lymph node). Case 2 received ICT + Surgery + CRT.

statistically significant.

Results

Clinicopathological characteristics

Eventually, 120 well-documented patients were included in final analysis (Table 1). The median follow-up time was 20 months (ranged from 1 to 56 months). There were thirty-five patients died, the death rate was 29.2%. Twenty-seven patients died of tumor progression, and 8 patients died of disease-related or treatment-related complications described as follows: 3 patients died of respiratory failure due to pulmonary infection, 2 patients died of sudden unconsciousness, 2 patients died of sudden dyspnea, and 1 patient died of cervical hemorrhage.

Response of ICT

After two courses of ICT, tumor loci were evaluated by CT or MRI according to RECIST 1.1 criteria. There were 19 patients (11 in group A, 8 in group C) received CR, 85 patients (45 in group A, 27 in group B, 13 in group C) received PR, and 16 patients (1 in group A, 15 in group B) maintained SD of primary tumor. 1 patient from group A received CR, 85 patients (47 in group A, 23 in group B, 15 in group C) received PR, 23 patients (3 in group A, 14 in group B, 6 in group C) maintained SD, and 1 patient from group B reached PD of metastatic cervical lymph nodes. In addition, 10 patients were assessed as cN0 (Table 2).

LR and DM

Twenty patients in Group A, 11 in Group B, and 9 in

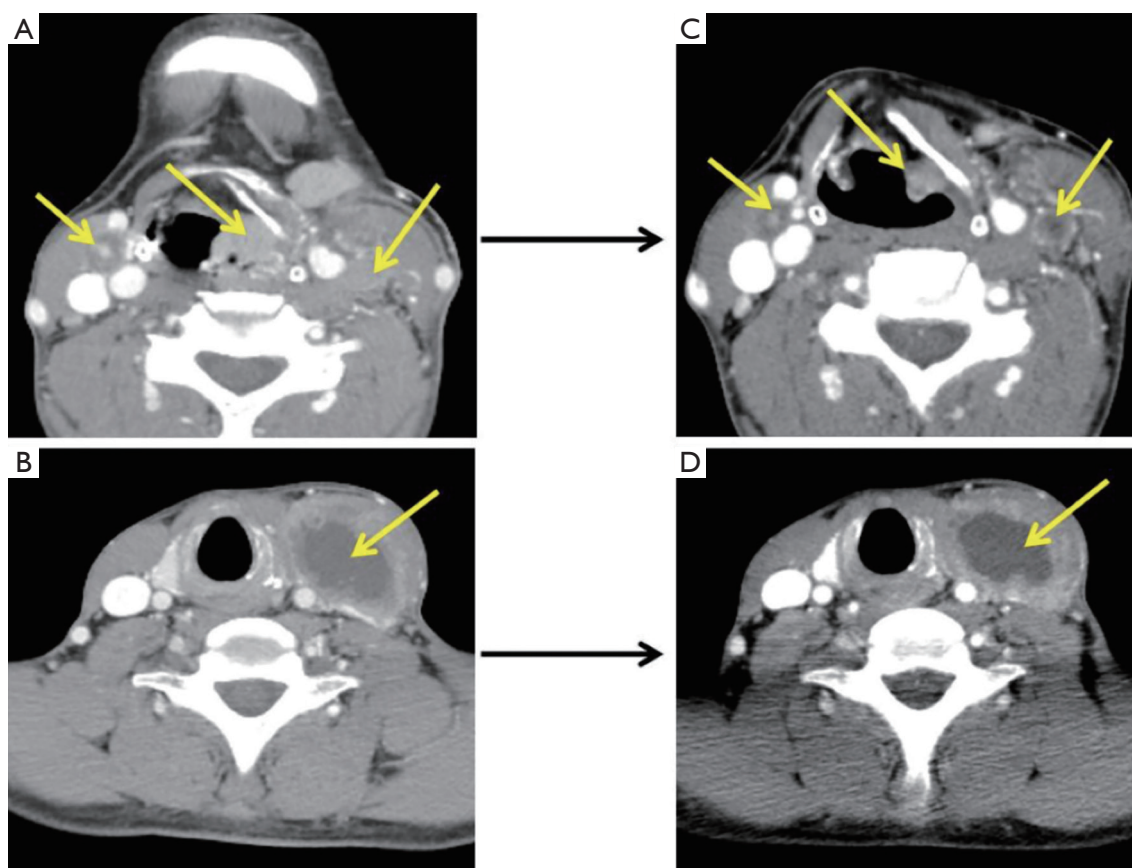


Figure 4 Typical case 3: before therapy, CT scan showed the tumor of left hypopharynx and the metastatic lymph nodes in bilateral neck (A,B, yellow arrow in the middle showed the primary tumor, yellow arrows on both sides showed the metastatic lymph nodes); after 2 courses of ICT, CT scan showed the primary tumor significantly achieved PR, while the metastatic lymph nodes maintained SD (C,D, yellow arrow in the middle showed the primary tumor, yellow arrows on both sides showed the metastatic lymph nodes). Case 3 received ICT + PND + CCRT.

Group C developed LR. Six patients in Group A, 13 in Group B, and 2 in Group C developed DM. The main site of DM was lung, followed by the bone and liver, and skin metastasis was rare. There was no significant difference in the LR among three groups. The incidence of DM in Group B was significantly higher than Group A ($P < 0.05$) and was probably higher than Group C ($P = 0.06$) (Table 3).

Supplementary treatment

There were totally forty patients suffered LR, 21 of whom received salvage operations. Twelve patients (5 cervical lymph nodes recurrence and 7 local tumor recurrence) were well controlled after surgery.

Survival outcome

Sixteen (28.1%) patients in Group A, 12 (28.6%) in Group B, and 7 (33.3%) in Group C died in our research, there was no significant difference in the mortality among three groups ($P = 0.897$). The total 3-year OS was 69.7%. In Group A, Group B and Group C, the 3-year OS was 69.7%, 72.9%, and 65.5% respectively. Neither, there was no significant difference in OS (see Figure 5).

Discussion

Locally advanced SCCHN usually has a poor prognosis, of which the reported 5-year OS is about 50% or even lower. The majority of patients will develop LR and/or DM,

Table 2 Response of induction chemotherapy of three groups

Characteristic	Group A (ICT + CCRT)	Group B (ICT + surgery + RT/CRT)	Group C (ICT + PND + CCRT)
N	57	42	21
CR (PT/LN)	11/1	0/0	8/0
PR (PT/LN)	45/47	27/23	13/15
SD (PT/LN)	1/3	15/14	0/6
PD (PT/LN)	0/0	0/1	0/0
cN0*	6	4	0

*, 10 patients were assessed as cN0 by CT and/or MRI image before initial treatment. ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; PND, planned neck dissection; PT, primary tumor; LN, lymph node.

Table 3 Locoregional recurrence and distant metastasis of three groups

Characteristic	Group A (ICT + CCRT)	Group B (ICT + surgery + RT/CRT)	Group C (ICT + PND + CCRT)	P value
N	57	42	21	
Local recurrence	13 (22.8%)	6 (14.3%)	6 (28.6%)	0.370
Regional recurrence	12 (21.1%)	6 (14.3%)	4 (19.0%)	0.688
Locoregional recurrence	20 (35.1%)	11 (26.2%)	9 (42.9%)	0.387
Distant metastasis	6 (10.5%)	13 (31.0%)	2 (9.5%)	0.011*

*, P=0.011<0.05: Group B vs. Group A. ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; PND, planned neck dissection.

especially within the first 2 years after primary therapy (5,6). In our research, the total LR rate was 33.3% (40/120), and the median time of LR was 8 months. The success rate of salvage operation was only about 50%.

ICT, though does not show benefit in extending OS, has already been firmly proven to decrease tumor stage, improve surgical resection, preserve organ functions, and reduce DM (2-4,7). Platinum-based combination chemotherapy regimens have been widely used in clinical practice. In recent years, a number of clinical trials have confirmed that TPF regimen (docetaxel, cisplatin and 5-fluorouracil) may achieve a higher

rate of remission without significantly increasing severe adverse reactions (2,8-10). Currently, TPF regimen is becoming the first choice of ICT for locally advanced SCCHN.

Another important role of ICT is to predict the effectiveness of subsequent radiation/chemoradiation therapy (11,12). According to NCCN guideline, the efficacy of ICT determines the use of following treatment. Patients with complete remission (CR) after primary therapy will receive radical RT or CCRT, and patients with partial remission (PR) may receive CCRT or surgery. For those without remission, surgery should be the proper option. In this study, the remission rates of primary tumor were 94.9% in Group A, 62.8% in Group B, and 95.5% in Group C, respectively.

In subgroup analysis, the courses of ICT before CCRT did not affect the outcome. The LR, DM and OS were comparable between patients receiving ≤2 courses of ICT and those undergoing ≥3 courses of ICT. This was consistent with previously reported (13). However, there were evidence showing that the frequency of ICT may affect the prognosis (14,15). Indeed, for patients tolerable to ICT, 2 to 4 courses before RT or CRT are acceptable.

Of note, metastatic cervical lymph nodes are less sensitive to ICT than primary tumors, which might be ascribed to the different biologic characteristics. In this study, the lymph nodes remission rates were 84.8% in Group A, 53.5% in Group B and 68.2% in Group C, respectively. Patients in Group C received ND before RT (so-called planned neck dissection, PND). Some research showed that ND before RT can improve DFS and PFS (16-18). In another research of our department, we found priority of PND before RT in regional control for those with lymph nodes metastases insensitive to ICT (19). Moreover, the effectiveness of ICT can be further determined by pathological examination of lymph nodes, by which the radiation dose of cervical lymphatic drainage area can be calculated precisely so as to reduce the complications.

In the present study, the DM rate of Group B was significantly higher than Group A, and also, although not significantly, higher than Group C. We can infer that patients have poor response to chemotherapy might occur recurrence and metastasis easier. However, the death rate and the 3-year OS of Group B were not worse than other two groups, which was attributed to second-line chemotherapy, molecule-targeted therapy (Cetuximab, Nituzumab, or Bevacizumab), and the best supportive treatments including nutrition and analgesia (20-22).

Both international guideline and domestic expert consensus recommend MDT collaboration in the treatment of stage III, IVA, and IVB patients. In our institution,

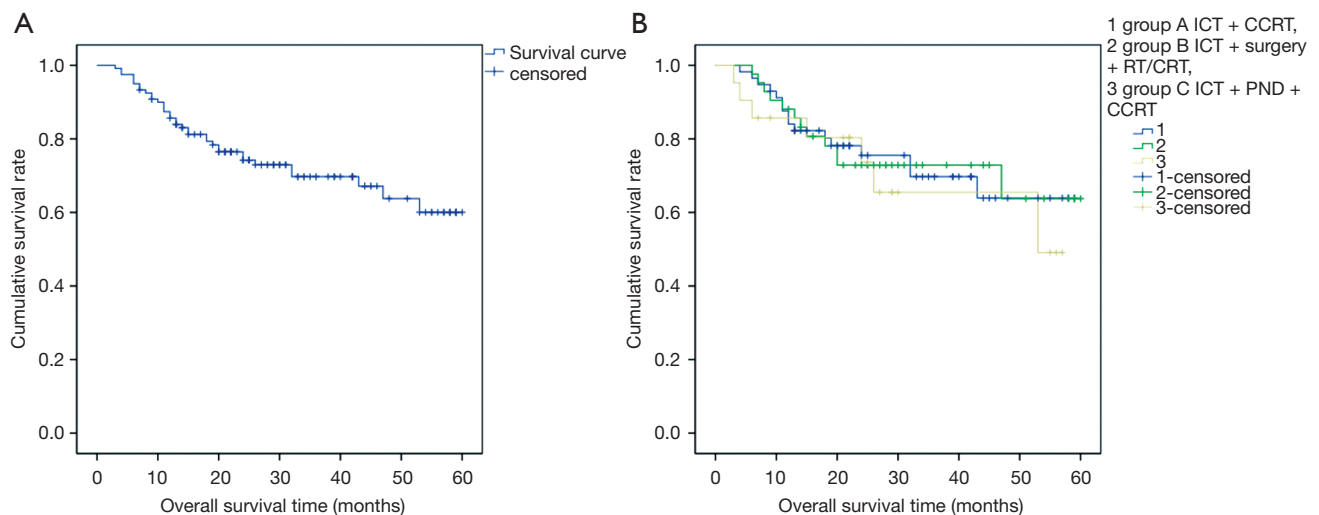


Figure 5 Survival curve of all enrolled patients (A). Kaplan-Meier curves showed there was no significant difference among three groups (Log rank test, $P=0.835$) (B). ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; PND, planned neck dissection.

Individualized therapeutic plan has been made in consideration of tumor stage, physical performance, organ function preservation, financial status, and cultural customs.

Conclusions

In conclusion, for patients with locally advanced SCCHN, the integrity and thoroughness of primary treatment is very important. Individualized therapeutic regimen based on the response of ICT could be an ideal solution. As metastatic cervical lymph nodes are less sensitive to ICT than primary tumors, PND before CCRT might improve the regional control, preserve throat function, and lead to better quality of life. A MDT collaboration is necessary throughout the treatment process.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.12.44>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study had been approved by the Ethics Committee of our Hospital [zjzlyy Medical Ethics Approval Document (2015)-01-21]. Informed consent was waived due to the retrospective nature of the study.

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