Concurrent Definitive Chemoradiation Incorporating Intensity-Modulated Radiotherapy Followed by Adjuvant Chemotherapy in High Risk Locally Advanced Cervical Squamous Cancer: A Phase Ⅱ Study.

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Abstract

Background

Although the prognosis of locally advanced cervical cancer has improved dramatically, survival for those with stage □B-□A disease or lymph nodes metastasis remains poor. It is believed that the incorporation of intensity-modulated radiotherapy into the treatment of cervical cancer might yield an improved loco-regional control, whereas more cycles of more potent chemotherapy after the completion of concurrent chemotherapy was associated with a diminished distant metastasis. We therefore initiated a non-randomized prospective phase□ study to evaluate the feasibility of incorporating both these two treatment modality into the treatment of high risk locally advanced cervical cancer.

Objectives

to determine whether the incorporation of intensity-modulated radiotherapy and the addition of adjuvant paclitaxel plus cisplatin regimen into the treatment policy for patients with high risk locally advanced cervical cancer might improve their oncologic outcomes.

Study Design:

Patients were enrolled if they had biopsy proven stage □A-□A squamous cervical cancer or stage □B disease with metastatic regional nodes. Intensity-modulated radiotherapy was delivered with dynamic multi-leaf collimators using 6MV photon beams. Prescription for PTV ranged from 45.0 ~ 50.0Gy at 1.8Gy ~ 2.0Gy/fraction in 25 fractions. Enlarged nodes were contoured separately and PTV-nodes were boosted simultaneously to a total dose of 50.0–65 Gy at 2.0- 2.6Gy/fraction in 25 fractions. A total dose of 28 ~ 35Gy high-dose- rate brachytherapy was prescribed to point A in 4 ~ 5 weekly fractions using an iridium- 192 source. Concurrent weekly intravenous cisplatin at 30mg/m^2 was initiated on the first day of radiotherapy for over 1-hour during external-beam radiotherapy. Adjuvant chemotherapy was scheduled within 4 weeks after the completion of concurrent chemo-radiotherapy and repeated 3 weeks later. Paclitaxel 150 mg/m^2 was given as a 3-hour infusion on day1, followed by cisplatin 35 mg/m^2 with 1-hour infusion on day1-2 (70 mg/m^2 in total).

Results

Fifty patients achieved complete response 4 weeks after the completion of the treatment protocol, whereas 2 patients had persistent disease. After a median follow-up period of 66 months, loco-regional (including 2 persistent disease), distant, and synchronous treatment failure occurred in 4 ,5, and 1, respectively. The 5-year disease-free survival, loco-regional recurrence-free survival, distant-metastasis recurrence-free survival was 80.5%, 90.3%, and 88.0%, respectively. Four of the patients died of the disease, and the 5-year overall survival was 92.1%. Most of the toxicities reported during concurrent chemo-radiotherapy were mild and transient. The occurrence of hematological toxicities elevated mildly during adjuvant chemotherapy, as 32% (16/50) and 4% (2/50) patients experienced grade 3–4 leukopenia and thrombocytopenia, respectively. Grade 3–4 late toxicities were reported in 3 patients.

Conclusions

The incorporation of intensity-modulated radiotherapy and adjuvant paclitaxel plus cisplatin chemotherapy were highly effective and well-tolerated in the treatment of high-risk locally advanced cervical cancer. The former yields an improved loco-regional control, whereas distant metastases could be effectively eradicated with mild toxicities when adjuvant regimen was prescribed.

Highlights

1. Incorporating IMRT and adjuvant chemotherapy into the treatment of locally advanced cervical cancer is highly effective.
2. IMRT is associated with a reduced loco-regional relapse.
3. Adding adjuvant TP chemotherapy could diminish tumor hematological spread.
4. Toxicity profiles were mild and manageable.

Introduction

Although the prognosis of locally advanced cervical cancer (LACC) has improved dramatically, survival for those with stage □B-□A disease or lymph nodes metastasis (LNM) remains poor. If treated with conventional radiotherapy alone, approximately 46%~78% stage □B-□A disease would relapse at 5 years, and the outcomes for those with LNM seemed to be worse [1–5]. Even after concurrent chemoradiotherapy (CCRT) became the standard of care for LACC, nearly 50% of this subgroup of patients would develop treatment failure [6–8]. Thus, this subgroup of patients was classified as “high-risk”.

In recent decades, intensity-modulated radiotherapy (IMRT) has become the mainstream of treatment for patients with prostate, rectal, neck, and several other malignancies [9–12]. Theoretically, its incorporation into the treatment of LACC might yield an improved loco-regional control as well, as it allows for an escalated prescription dose to target volumes while sparing normal tissues from excessive radiation. However, several concerns still exist, including prolonged treatment time, geographical target miss, organ motion and set-up errors, etc. Therefore, further evidence supporting its regular use in the treatment of LACC is warranted.

Potential benefit of adjuvant chemotherapy following CCRT could firstly be implied in the reports published by Morris et al., who revealed that patients prescribed with more cycles of higher dose chemotherapy demonstrated a diminished risk of distant metastasis (DM) [13]. Nevertheless, investigations carried out thereafter were mainly phase trials composed of heterogeneous patients treated with various cytotoxic combinations, thus conflicting and ambiguous results were usually reported [14–21].

We therefore initiated a non-randomized prospective phase study to investigate whether the incorporation of IMRT and adjuvant paclitaxel plus cisplatin (TP) regimen, which had been revealed to be the most, or at least one of the most active cytotoxic combinations in the treatment of advanced or recurrent cervical cancer [22], would improve the treatment outcome of high-risk LACC patients. The primary endpoints of this study were disease-free survival (DFS) and overall survival (OS). The secondary endpoints included the patterns of failure and toxicity profiles.

Materials And Methods

Eligibility

Patients were enrolled if they had biopsy proven stage A-A squamous cervical cancer or stage B disease with metastatic regional nodes. Tumor staging was defined according to the International Federation of Obstetrics and Gynecology (FIGO) system. Lymph nodes were classified as metastatic based on their radiographic findings (≥ 1.0cm in the short-axis dimension). Eligibility criteria also included: age ≤ 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1, no previous history of chemotherapy or radiotherapy, sufficient bone marrow, adequate renal and hepatic functions. Patients with synchronous malignancies, distant metastases, known hypersensitivity to cisplatin or paclitaxel, or those with poorly controlled medical conditions would be excluded.

Pretreatment workup

Pretreatment workup included detailed medical history, gynecological examination, complete blood count, blood chemistry, and chest X-ray. Lymph node involvement and parametrial infiltration were evaluated by magnetic resonance imaging (MRI) and/or abdomino-pelvic computer tomography (CT), and the former was preferred. If rectal or bladder invasion were suspected, additional rectoscopy or cystoscopy would be performed. Written informed consents was required prior to the initiation of medical intervention. The study was approved by the Institutional Review Board and abided with the ethical standards of the Helsinki Declaration on good clinical practice (Registration No.: LC2010B33).

Treatment schedule

Treatment schedule was outlined in Fig. 1. IMRT was delivered with dynamic multi-leaf collimators using 6MV photon beams. A 5mm slice thickness CT simulation was carried out in the supine position. A comfortably full bladder and empty rectum were required, and both oral and intravenous administrations of contrast agents were used.

Planning was performed using the Pinnacle3 9.0 treatment planning systems (Philips Healthcare, Andover, MA, USA). Clinical target volume (CTV) was defined as the gross tumor plus areas potentially containing microscopic disease, generally consisting of a 1–2 cm margin around the cervix, uterus, parametria, presacral space, lymph drainage area, and superior third of the vagina. The common iliac, external iliac, internal iliac and obturator nodal volume was contoured based on the contrast-enhanced vessels with a 7mm circumferential margin. In patients with bulky pelvic LNs (> 2cm in shortest axis) or involved common iliac nodes or beyond, it would be contoured to the level of renal arteries (extended field-MIRT, EF-IMRT); otherwise, it would be 2-3cm above the aortic bifurcation.

The CTV was expanded by 5mm uniformly to create the planning target volume (PTV). Prescription for PTV ranged from 45.0 ~ 50.0Gy at 1.8Gy ~ 2.0Gy/fraction in 25 fractions. Involved nodes were contoured separately and were defined as GTV-nodes. A tailored margin of 3mm was added to GTV-nodes to generate PTV-nodes, which were treated with a simultaneous integrated boost (SIB) technique to a total dose of 50.0–65 Gy at 2.0-2.6Gy/fraction in 25 fractions.

Brachytherapy was initiated when 27.0 ~ 30.0 Gy of external beam was delivered to PTV. The aim of brachytherapy boost was to deliver cumulative EQD2 doses (combined external beam radiotherapy (EBRT) and brachytherapy delivered in 2Gy equivalent doses) of ≥ 80 Gy to point A for stage B-A disease and ≥ 90 Gy for stage B-A disease. Specifically, a total dose of 28 ~ 35Gy high-dose- rate (HDR) brachytherapy was prescribed to point A in 4 ~ 5 weekly fractions using an iridium- 192 source. An additional fraction of 5-7Gy brachytherapy would be delivered if residual cervical tumor was suspected by pelvic examination or MRI.

Chemotherapy consisted of 4 ~ 6 cycles of concurrent cisplatin infusions and 2 cycles of adjuvant TP regimen. Concurrent weekly intravenous cisplatin at 30mg/m^2 was initiated on the first day of radiotherapy for over 1-hour during EBRT. Adjuvant chemotherapy was scheduled within 4 weeks after the completion of CCRT and repeated 3 weeks later. Paclitaxel 150 mg/m^2 was given as a 3-hour infusion on day1, followed by cisplatin 35 mg/m^2 with 1-hour infusion on day1-2 (70 mg/m^2 in total). Discontinuation of chemotherapy was allowed in the event of grade 3–4 hematological or gastrointestinal toxicities. It would be resumed when patients' absolute neutrophil count recovered to ≥ 1500/mm^3 and their platelet count improved to ≥ 100,000/mm^3; however, doses of all agents should be subsequently reduced by 20%.

Toxicity assessment

The patients were assessed for toxicities twice per week during treatment. Complications occurred within 90 days of the initiation of chemoradiation were classified as acute complications, whereas those occurred afterwards were classified as late complications. The severity of acute complications was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Late complications were graded according to the Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Scheme.

Follow up

Post-treatment response was assessed based on pelvic examination and pelvic MRI or CT 4 weeks after the completion of treatment schedule. Continued surveillance was conducted at 3-month intervals for 2 years, every 6 months during the next 3 years, and annually thereafter. At each follow-up visit, pelvic examination including Pap smear and HPV detection was routinely performed, whereas imaging including ultrasound, chest x-ray, CT, or MRI were prescribed at physician’s discretion.

Patterns of failure were analyzed in terms of loco-regional recurrence (LRR) and distant metastasis (DM). LRR was defined as persistent disease or any recurrence in cervix, uterus, vagina, adjacent pelvic structures, or regional lymph nodes including pelvic or para-aortic LNs. DM was defined as recurrence occurred in non-regional LNs or visceral metastases.

Statistics

Disease-free survival (DFS), loco-regional recurrence free survival (LRRFS), distant metastasis free survival (DMFS), and overall survival (OS) was defined from the time of diagnosis to the time of first evidence of relapse or death from any cause. Patients without documented evidence of recurrence were censored at the date of last follow up visit. Cumulative survival rate was calculated with the Kaplan-Meier method using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). Toxicities are reported as counts with percentages.

Results

Patients characteristics

Between July 2010 and January 2013, 52 eligible patients were enrolled. Patient characteristics are summarized in Table 1. Median age of these patients was 55 years (range: 39–67 years). The number of patients with stagB, A, B, and A disease was 16, 0, 34, and 2, respectively. Thirty-nine patients had radiologically enlarged pelvic lymph nodes (PLNs) evaluated to be metastatic, among which 10 had synchronous para-aortic lymph nodes (PALNs) metastasis.

Table 1
Patients characteristics

Characteristics	values
Median age (range)-years	55 (39 ~ 67)
ECOG	
0	43
1	9
International FIGO Stage-No. (%)	
IIB	16
IIIA	0
IIIB	34
IVA	2
Tumor Grade-No. (%)	
Well-differentiated	5
Moderately-differentiated	22
Poorly-differentiated	18
Not specified	7
Median diameter of primary tumor (range)-cm	5 (3–7)
Pelvic lymph nodes involvement -No. (%)	
positive	39
negative	13
Paraaortic lymph nodes involvement -No. (%)	
positive	10
negative	42
Median of the shortest diameter of LNs (range)-cm	1.2 (1.0-3.7)
Median cumulative point A EQD2 doses (range)-Gy	
IIB	93.8 (83.9 ~ 93.8)
IIIB ~ IVA	99.6 (93.8 ~ 109.5)
Median duration of OTT of radiotherapy-days	46.5 (42–66)
Median cycles of concurrent chemotherapy	5 (1–6)
Median cycles of adjuvant chemotherapy	2 (1–3)

Radiotherapy

All the 52 patients completed intended radiation schedule. A median of 50Gy was prescribed to the PTV (range, 45-50Gy), whereas PTV-nodes were boosted to a median of 60Gy (range, 50.0-65Gy). EF-IMRT was administered in 22 patients, including 10 with positive PALNs and 12 treated prophylactically.

A median of 5 fractions (range, 4–6) of brachytherapy boost were prescribed. The median cumulative EQD2 doses prescribed to point A was 93.8 Gy (range, 83.9 ~ 93.8Gy) for patients with stage IIB disease and 99.6 Gy (range,93.8 ~ 109.5Gy) for those with □B-□A disease, respectively.

The median overall treatment time (OTT), including the duration of EBRT and brachytherapy, was 46.5 days (range, 42–66 days). Radiotherapy interruption exceeding 3 days was documented in 5 patients, among which 3 were related to delayed recovery of myelosuppression and 2 were related to acute gastrointestinal toxicities.

Chemotherapy

A total of 257 cycles of concurrent cisplatin were administered with a median of 5 cycles (range, 1–6 cycles), and the majority (79%) of patients completed 5–6 cycles. Two patients discontinued concurrent cisplatin within 2 cycles, one related to grade 3 vomiting at first cycle and the other related to grade 3 myelosuppression occurred at 2nd cycle of chemotherapy.

A total of 50 patients received adjuvant chemotherapy, while above mentioned 2 patients who discontinued concurrent chemotherapy declined further medical intervention and withdrew from the trial. Thirty-nine (78%) patients completed planned 2 cycles of adjuvant chemotherapy. Two patients received only 1 cycle due to grade 3 thrombocytopenia. As for the remaining 9 patients, serum squamous cell carcinoma antigen (SCCA) levels did not return to normal until 3rd cycle was administered. Median interval between the completion of CCRT and the initiation of adjuvant chemotherapy was 26 days (range, 23 ~ 35 days).

Outcomes

Fifty patients achieved complete response (CR) 4 weeks after the completion of the treatment protocol, whereas the remaining 2 had persistent disease. After a median follow-up of 66 months (range, 17–97 months), 42 patients were still alive without disease. Detailed information of treatment failure was listed in Table 2. In brief, loco-regional (including 2 persistent disease), distant, and synchronous treatment failure occurred in 4 ,5, and 1, respectively. The 5-year DFS, LRRFS, DMFS was 80.5%, 90.3%, and 88.0%, respectively.

Table 2
First site of treatment failure (including persistent disease)

First site of recurrence	No. of patients (%)
Loco-regional recurrence	4
Persistent disease	2
Vagina	1
PALN outside radiation field	1
Distant metastasis	5
Lung	1
Lung and liver	1
Mediastinum or supraclavicular LNs	3
Synchronous LRR and DM	1
Synchronous pelvic side-wall, PLN, PALN, and supraclavicular LNs	1

Four of the patients succumbed to the disease, including 2 with persistent disease, 1 with hematological relapse, and 1 with synchronous relapse. The remaining patients were successfully salvaged, as 1 vaginal relapse salvaged by surgery, 1 pulmonary metastasis by chemotherapy, and all the 4 lymphogenous recurrence occurred in radiation-naïve nodes and were salvaged by radiotherapy. The 5-year OS was 92.1%. The survival curves were shown in Fig. 2 ~ 5.

Toxicities

The incidence and categories of toxicities are summarized in Table 3 ~ 4. In brief, gastrointestinal and hematological toxicities were mostly reported acute complications during CCRT, which were usually mild and transient. The occurrence of hematological toxicities elevated mildly during adjuvant chemotherapy, as 32% (16/50) and 4% (2/50) patients experienced grade 3–4 leukopenia and thrombocytopenia, respectively. Yet, none of the patients developed febrile episodes or required blood transfusion. Delayed chemotherapy schedules and reduced dosage was required in 14 patients (28%) and 4 patients (7.7%), respectively. Grade 3–4 late toxicities were reported in 3 patients, including 1 vesicovaginal fistula, 1 recto-vaginal fistula, and 1 intestine obstruction requiring surgical intervention.

Table 3
Acute toxicity of CCRT and adjuvant chemotherapy

Toxicities	CCRT (n = 52)					Adjuvant chemotherapy (n = 50)				
	Grade0	Grade1	Grade2	Grade3	Grade4	Grade0	Grade1	Grade2	Grade3	Grade4
Hematologic toxicity										
Neutropenia	8(15.4%)	9(17.3%)	29(55.8%)	6(11.5%)	0(0%)	6(12.0%)	8(16.0%)	20(40.0%)	15(30.0%)	1(2.0%)
Febrile neutropenia	52(100%)	0(0%)	0(0%)	0(0%)	0(0%)	50(100.0%)	0(0%)	0(0%)	0(0%)	0(0%)
Anemia	27(51.9%)	13(25.0%)	12(23.1%)	0(0%)	0(0%)	20(40.0%)	6(12.0%)	24(48.0%)	0(0%)	0(0%)
Thrombocytopenia	49(94.2%)	2(3.8%)	1(1.9%)	0(0%)	0(0%)	33(66.0%)	11(22.0%)	4(8.0%)	2(4.0%)	0(0%)
Non-hematologic toxicity										
Nausea/vomiting	0(0%)	34(65.4%)	14(26.9%)	4(7.7%)	0(0%)	0(0%)	36(72.0%)	12(24.0%)	2(4.0%)	0(0%)
Diarrhea	35(67.3%)	11(21.2%)	4(7.7%)	2(3.8%)	0(0%)	45(90.0%)	3(6.0%)	2(4.0%)	0(0%)	0(0%)
Bladder toxicity	44(84.6%)	6(11.5%)	2(3.8%)	0(0%)	0(0%)	50(100%)	0(0%)	0(0%)	0(0%)	0(0%)
Hepatologic	50(96.2%)	2(3.8%)	0(0%)	0(0%)	0(0%)	47(94.0%)	2(4.0%)	1(2.0%)	0(0%)	0(0%)
Renal	51(98.1%)	1(1.9%)	0(0%)	0(0%)	0(0%)	49(98.0%)	1(2.0%)	0(0%)	0(0%)	0(0%)

Table 4
Late treatment-related toxicities

	No. of patients				
Toxicities	Grade0	Grade1	Grade2	Grade3	Grade4
Gastrointestinal	19	24	7	0	2
Genitourinary	36	13	2	0	1

Discussion

Principal findings:

As far as we know, the current study represents the first publication investigating the efficacy and safety of incorporating IMRT and adjuvant TP regimen into the treatment of high risk LACC patients. We found that such a paradigm was associated with a markedly improved survival with well-tolerated side effects, as estimated 5-year OS, DFS, LRRFS, and DMFS was 92.1%, 80.5%, 90.3%, and 88.0%, respectively, which compared favorably with most previous reports composed of similar study population.

In the early years, a median of summed EQD2 dose of 77.1 Gy had been used, which was soon proved to be insufficient for bulky tumors [23]. In a recent study, Meng et al. revealed that higher EQD2 dosage to Point A (≥ 98Gy) was associated a significant LRRFS advantage [24]. In our series, a median EQD2 of 93.8Gy for stage □B-□A patients and 99.6Gy for stage □B-□A yielded a complete response of 96.2%, reiterating that higher radiation dosage prescribed to point A still constitutes the cornerstone for the definitive treatment of LACC even in the era of modulated radiotherapy.

It has been reported that approximately 40% patients with adenopathy were not able to obtain a complete nodal response if treated with conventional radiotherapy, and 46.2% of them would recur at 2 years [25]. By contrast, nearly 90%-100% involved nodes resolved completely when IMRT boost was used, and only 0%-8% of them relapsed [23, 26–29]. Consistently promising results were reported in the current study when a median IMRT boost of 60Gy was prescribed. All the involved nodes remised completely, and only one in-field regional relapse occurred synchronously with pelvic and distant recurrence. These findings suggested that IMRT boost was highly effective in nodal sterilization; it should be considered as an indispensable component of treatment for LACC, especially when positive nodes were present.

Except for escalated radiation dosage, SIB technique might be another underlying reason for improved loco-regional control, as it allowed for a maximum of 65Gy EBRT to be delivered at 2.6Gy per fraction within a median OTT of 46.5 days [30]. In Guckenberger' study, increased dose per fraction and reduced OTT through SIB allowed for an iso-toxic dose escalation of 8.0 Gy on average, which consequently yielded an improved tumor control probability from 15–28% [31]. It had been recommended that radiotherapy should be completed within 56 days so that potential accelerated cancer cell repopulation could be avoided [32–34]. In an undergoing multicenter study aiming to benchmark a high level of disease control, SIB was regarded as an evolution over the past decades and required in all the participants with pathologic nodes [35]. Its beneficial effect is expected to be further verified.

Occult paraaortic metastases might occur in approximately10 ~ 20% patients with apparently negative PALNs [36–37]. Yet, Lee et al. revealed that it was in patients with common iliac or > 3 pelvic LNs involvements that EF-IMRT was associated with a superior PALNs recurrence free survival over standard pelvic radiation (100% vs. 56.8%). By contrast, no significant survival difference was observed (100% vs. 93.8%) in patients without these features [29]. Based on these findings, the authors postulated that a risk-guided EF-IMRT seem to be more reasonable. In the present study, EF-IMRT was reserved for patients with involved common iliac nodes or bulky PLNs. Our reported 5-year PALNs recurrence free survival of 97.9% further validated the highly effectiveness of such a risk-guided policy in the management of paraaortic lymph-node metastasis.

The value of adjuvant chemotherapy might had been underestimated in previous literatures when stage I-� patients were enrolled[15, 16]. It was in a study made up of 48.7% stage �-� patients and 70% patients with LNM that a discernable DMFS advantage (20.5% vs. 30.8%) in favor of consolidating cisplatin plus 5-fluorouracil regimen was observed[17]. Further improved outcomes were reported when more potent cytotoxic combinations were used. In Zhang's paper, adjuvant paclitaxel plus nedaplatin (TN) regimen was associated with a 3% occurrence of DM in a cohort containing 70% stage � patients [21]. In our current series composed entirely of high-risk patients, adjuvant TP regimen led to a 5-year DMFS of 88.0%, which compared favorably with previously reported data achieved in similar population. These observations indicated that in high-risk LACC patients, adjuvant paclitaxel-platinum combination chemotherapy might play an important role for reduced distant metastasis.

Several other first-line regimens for recurrent of metastatic cervical cancer had also been evaluated in the adjuvant setting with encouraging oncologic outcomes, including gemcitabine plus cisplatin (GP) or paclitaxel plus carboplatin (TC) regimen, etc. [18, 19]. However, nearly 90% of the participants prescribed with GP regimen experienced grade 3–4 complications including 2 possibly toxicity-related deaths, whereas TC -based CCRT followed by adjuvant chemotherapy was associated with a 60.0% occurrence of grade 3–4 acute hematological toxicity or even higher [18, 20]. In comparison, TP or TN regimen seem to be more tolerable, as severe hematological toxicities were reported to be 36% and 21.8% in the present study and in Zhang's study, respectively [21]. In this regard, TP or TN regimens seemed to be preferred adjuvant options following CCRT.

Yet, Choi et al. revealed that although hematological relapse was statistically reduced by adjuvant PF regimen, the occurrence of non-regional lymphogenous relapse remained unaffected [17]. In a series consisted entirely of patients with lymphadenopathy, Abe et al. even failed to disclose an improved DFS when adjuvant TC regimen was administered. [20]. A similar trend was observed in the current study, as hematological spread was diminished to the low of 3.8%, while out-field lymphogenous metastasis occurred in 9.6% of the patients. Therefore, further investigations should be focused on exploring novel agents more effective in sterilizing tumor cells harbored in lymph nodes.

Due to the relatively small study population and lack of valid control group, a selection bias could not be avoided in the current study. Besides, although designed to identify an optimal treatment regimen for advanced LACC, several emerging radiation techniques which might further improve therapeutic-ratio, such as pet-CT based planning and image-guided adaptive brachytherapy, were not included in the current study. Nevertheless, the strength of this study lies in that it represents the largest study composed homogeneously of high-risk patients treated with a well-established highly effective cytotoxic regimen, so that confounding effects of the enrollment of low-risk patients or less potent regimens were minimized.

Conclusions

This current study demonstrated that IMRT and TP chemotherapy were highly effective and well-tolerated in the treatment of high-risk LACC. By means of ensured target volume coverage, escalated nodal boosts, enhanced biological effects, and tailored radiation fields, IMRT yields an improved loco-regional control. Meanwhile, distant metastases could be effectively eradicated with mild toxicities when adjuvant TP regimen was prescribed. Larger prospective randomized controlled trial studies are warranted to further validate these findings.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of National Cancer Center/National Clinical Research center for Cancer/Cancer Hospital and abided with the ethical standards of the Helsinki Declaration on good clinical practice (Registration No.: LC2010B33).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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All authors have contributed significantly, and that all authors agree with the content of the manuscript.

Authors' information (optional)

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Figures

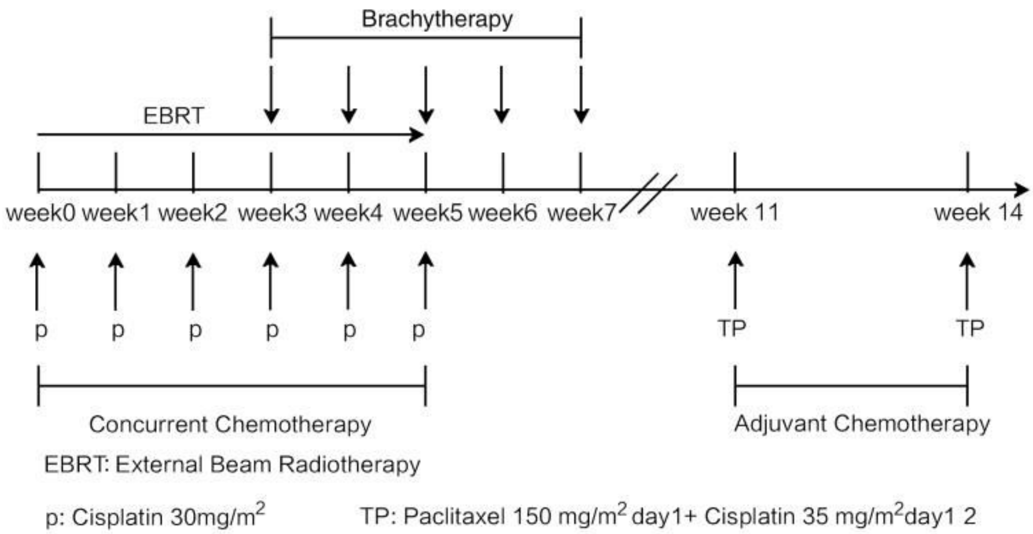

Figure 1

Treatment schedule for patients treated with concurrent CCRT incorporation IMRT followed by adjuvant TP regimen. EBRT External Beam Radiotherapy p: Cisplatin 30mg/m2 TP: Paclitaxel 150mg/m2 d1 + Cisplatin 35mg/m2 d1-d2

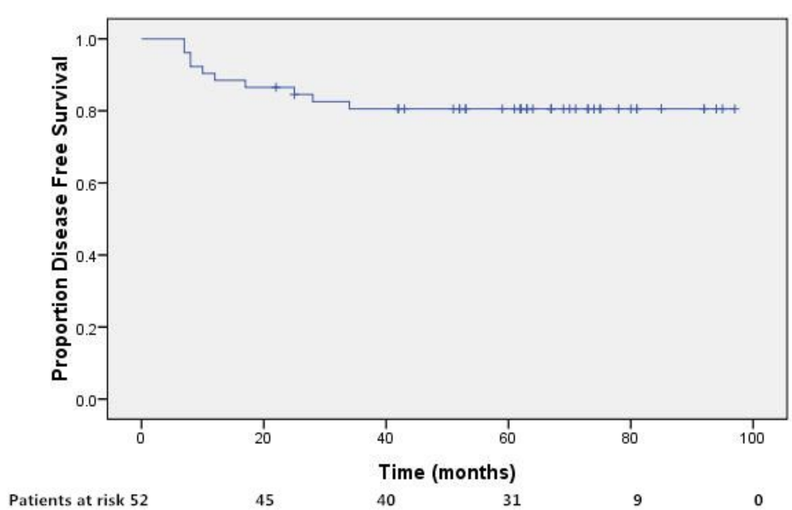

Figure 2

Disease free survival for patients treated with concurrent CCRT incorporation IMRT followed by adjuvant TP regimen. The 5-year disease-free survival was 80.5%.

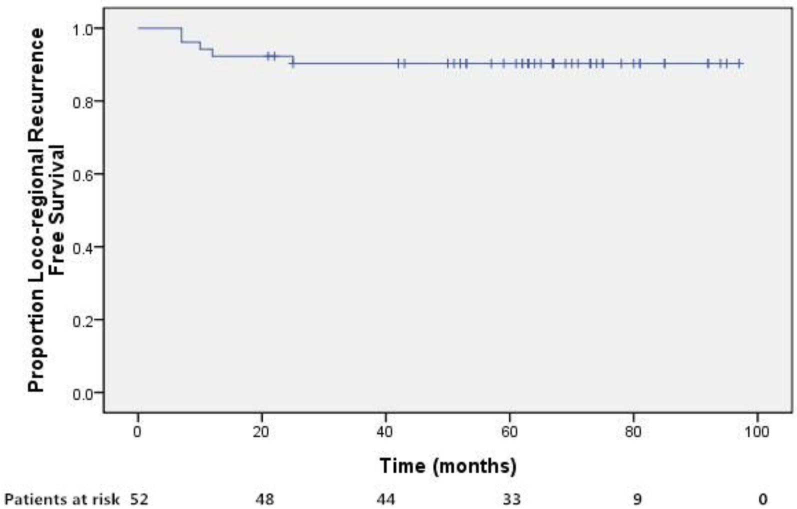

Figure 3

Loco-regional recurrence free survival for patients treated with concurrent CCRT incorporation IMRT followed by adjuvant TP regimen. The 5-year loco-regional recurrence-free survival was 90.3%.

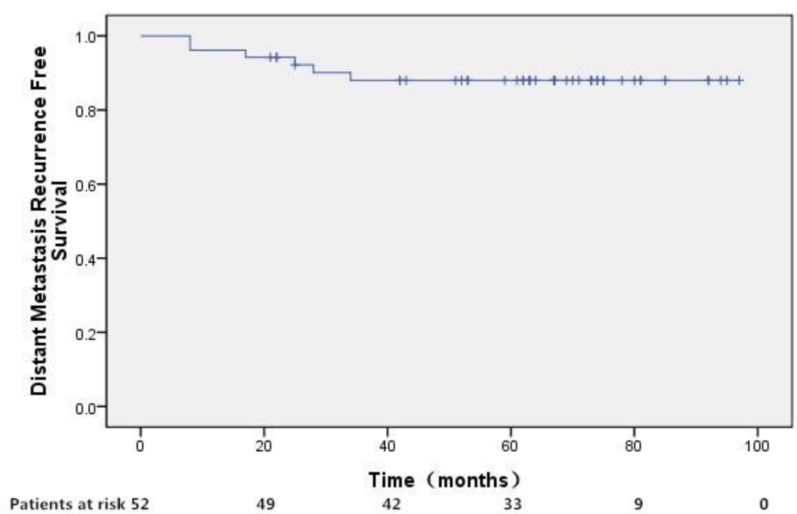

Figure 4

Distant metastasis free survival for patients treated with concurrent CCRT incorporation IMRT followed by adjuvant TP regimen. The 5-year distant-metastasis free survival was 88.0%.

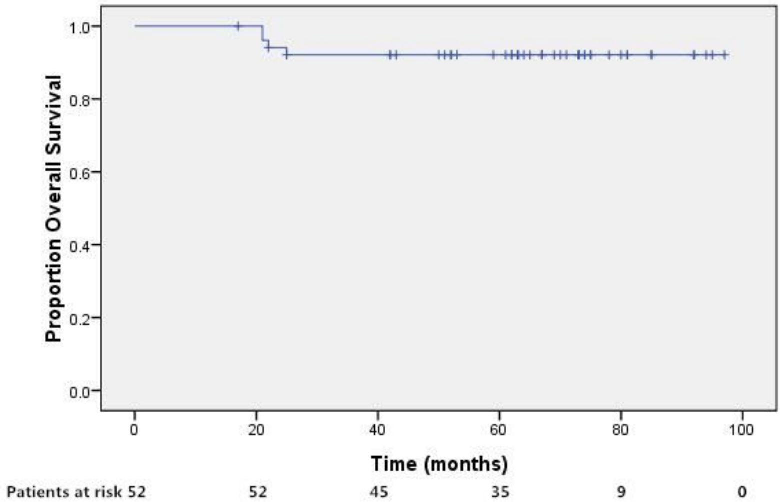

Figure 5

Overall survival for patients treated with concurrent CCRT incorporation IMRT followed by adjuvant TP regimen. The 5-year overall survival was 92.1%.