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ORIGINAL RESEARCH

The impact of the interval between the induction of chemotherapy and radiotherapy on the survival of patients with nasopharyngeal carcinoma

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Background: There have been no reliable scientific studies examining whether the interval between induction chemotherapy (IC) and initiating radiotherapy is associated with poor outcomes of nasopharyngeal carcinoma (NPC).

Patients and methods: In this retrospective study, we included a total of 239 local advanced NPC patients who underwent concurrent chemoradiotherapy and IC. Based on the interval between IC and intensity-modulated radiation therapy (IMRT), the patients were classified into three groups as follows: Group A (≤7 vs >7 days), Group B (≤14 vs >14 days), and Group C (≤ 21 vs >21 days). Univariate and multivariate regression analyses were performed to determine the prognostic factors of survival outcomes. The differences between the two groups were compared by the log-rank test.

Results: The median IC-IMRT interval was 9 days (range, 1–76 days). The median follow-up time was 40 months (range, 4–58 months). The IC-IMRT interval including Group A, Group B, and Group C was not significantly associated with overall survival (OS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRFS), or disease-free survival (DFS). Multivariate analysis showed that the tumor stage was the independent significant predictor for OS, DMFS, LRFS, and DFS. But it appears that there was a trend toward improvement in the outcome of ≤7 days group in OS from the Kaplan–Meier curves.

Conclusion: It is also feasible to postpone radiotherapy for 1–3 weeks if patients were unable to receive treatment immediately due to chemotherapy complications such as bone marrow suppression. However, we suggest that patients should start IMRT as soon as possible after IC.

Keywords: nasopharyngeal carcinoma, interval, induction chemotherapy, radiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck cancer in Southeast Asia.[1] Radiotherapy is the main treatment modality for NPC. With the advancement of imaging technology, the emergence of intensity-modulated radiation therapy (IMRT), and the application of concurrent chemotherapy in patients with advanced diseases, the survival rate of NPC patients has been significantly improved.[2]

Numerous research studies have revealed that induction chemotherapy (IC) followed by concurrent chemoradiotherapy was relatively safe and could achieve a better survival than concurrent chemoradiotherapy in NPC patients by reducing the risk of death, tumor progression, and distant metastasis.[3–5] The study of Phase III trial by Sun et al showed that the combination of radiotherapy and chemotherapy with IC in locally advanced NPC with high-risk T3-4N1/TxN2-3M0 can significantly improve

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the overall survival (OS), failure-free survival, and distant failure-free survival rate.[6]

Some oncologists try to give radiation therapy as soon as clinically possible after the IC, whereas others delay the use of radiation with an interval of 3 weeks after chemotherapy. However, patients occasionally face a delay in starting their radiotherapy due to many factors including comorbid medical diseases, chemotherapy complications, and availability of radiation facilities. In less developed areas such as Hainan Province with a rather high incidence of NPC and limited resources in many settings (such as a shortage of radiation oncologists and/or equipment), a delay in starting radiotherapy is a major public health problem.

Various studies have proposed that the interval time (IT) from surgery to adjuvant therapy (radiation or chemotherapy) can have an impact in many types of cancers such as breast, colorectal, endometrial, head and neck cancers, and glioblastoma.[7–11]

To date, there have been no reliable scientific studies examining whether the IT from IC to radiotherapy can be associated with poor survival outcomes of NPC. Neither has the optimal time from IC to initiating radiotherapy been examined. Thus, to address these research gaps, we performed a retrospective analysis to evaluate the effect of IT from IC to radiotherapy on oncological outcomes in patients with NPC. In this study, we define "interval time" as the time between the end of chemotherapy and the beginning of radiotherapy.

Patients and methods

Patients

We retrospectively analyzed the medical data of patients with NPC who underwent IMRT and IC between December 2013 and November 2015 at the Hainan General Hospital, Haikou, China. Patients were eligible for inclusion in this study if:

- the patients had stage III–IVb NPC;
- the patients had not received radiotherapy or chemotherapy before;
- IMRT was administered to the nasopharynx at a prescription dose of 68–72 Gy in 30–33 fractions;
- they finished radiotherapy on time;
- they underwent no adjuvant chemotherapy followed by IMRT;
- they had complete clinicopathological and follow-up data.

We ensured that all patients' information is anonymous before starting analysis. Two-hundred thirty-nine NPC patients were included in this study. All patients were staged according to the seventh edition of the International Union against Cancer Control/American Joint Committee on Cancer staging system. All patients provided informed consent before treatment. All patients underwent a complete pre-treatment evaluation, including medical history, physical examination, hematology and biochemistry, fiber optic nasopharyngeal biopsy, nasopharyngeal and cervical magnetic resonance imaging, chest X-ray, abdominal ultrasound, and Technetium-99m-methylene diphosphonate whole body bone scan.

Treatment

All patients were treated by definitive IMRT plus concurrent chemotherapy with IC. All patients were treated with IMRT and fixed with a custom head-to-neck thermoplastic cast, with the neck resting on the stent. High-resolution CT scan was performed at 2 cm (slicing thickness 3 mm) below the sternoclavicular joint. Target volume was delineated slice-by-slice on CT scan of treatment plan.

The prescribed doses were 68–72 Gy in 30–33 fractions to planning target volume (PTV) of primary gross tumor volume (GTV), 60–62 Gy to PTV of high-risk clinical target volume (CTV1), 64–70 Gy to PTV of GTV of involved lymph nodes (GTVnd), and 54–56 Gy to PTV of low-risk clinical target volume (CTV2).

All patients were delivered with the concurrent chemoradiation regimen every 3 weeks during radiotherapy. IC consisted of docetaxel plus cisplatin (or nedaplatin) or cisplatin (or nedaplatin) plus fluorouracil and concurrent chemoradiation consisted of platinum-based single or two drugs given every 3 weeks for one to three cycles during radiotherapy. The patients received IC plus concurrent chemotherapy for at least three cycles.

Follow-up

All patients were followed at regular intervals by our department after radiotherapy. These follow-ups were every 3 months during the first 2 years, every 6 months for the next 3 years, and annually thereafter. The primary end points were OS, locoregional relapse-free survival (LRFS), disease-free survival (DFS), and distant metastasis-free survival (DMFS). All intervals were calculated from the date of the beginning of therapy.

Statistical analyses

χ^2 test was used to assess the distribution and clinical characteristics of selected demographic variables. The survival curves of OS and DFS were calculated by the Kaplan–Meier method, and the differences between the two groups were compared by the log-rank test. Univariate Cox regression analysis was used to explore the risk factors of survival outcome. Using the Cox proportional hazard model, multivariate analysis of each prognostic variable was analyzed

by the backward stepwise (likelihood ratio) procedure. The statistical significance was $P<0.05$. All analyses were conducted in the 22.0 edition of IBM SPSS statistics.

Ethics statement

This retrospective study was approved by the ethics committee of the Hainan General Hospital, Haikou, China. Patient consent to review their medical records was not required by the ethics committee of the Hainan General Hospital as this is a retrospective study. No interventional therapy was implemented to the patients and will not affect the outcome of the patients. Data were deidentifed to protect patient information confidentiality and privacy. We declare that this study was conducted in accordance with the Declaration of Helsinki.

Results

Patient demographics and baseline characteristics according to interval category

The baseline characteristics of patients are provided in Table 1. Their average age was 47 years, and the median age was 48 years (range, 19–70 years). One-hundred ninety-four (81.2%) patients were male. All the pathological types were type II/III. There were 129 (54.0%) and 110 (46.0%) patients with stage III and IV diseases, respectively. There were 151 (63.2%) and 88 (36.8%) patients with 3 and 4–5 cycles of chemotherapy, respectively.

The median IC-IMRT interval was 9 days (range, 1–76 days). One patient had an interval of 76 days between rounds of treatment. At this point, his clinical stage was T1N2M0, but due to financial difficulties he could not afford radiotherapy after having two cycles of IC. This meant that by the time he and his family had raised enough money for the radiotherapy it was the Spring Festival (Chinese New Year) holiday, which resulted in the delay of 76 days mentioned earlier. However, with this patient it was found during subsequent checkups that 43 months after finishing his treatment there had been no recurrence or metastasis. Overall, the number of cases whose IT was >3 weeks was relatively small, and so the patient was not ruled out by us. A total of 25%, 50%, and 75% of the patients were distributed within 6, 9, and 16 days, respectively. Based on the interval between IC and IMRT, the patients were classified into three groups as follows: Group A (≤7 vs >7 days), Group B (≤14 vs >14 days), and Group

Table 1 Baseline characteristics of all 239 patients grouped the data by day on the interval between induction chemotherapy and initiating radiotherapy

Characteristics	n	Group A			Group B			Group C		
		≤7 days N=84 (%)	>7 days N=155 (%)	*P*-value*	≤14 days N=168 (%)	>14 days N=71 (%)	*P*-value*	≤21 days N=207 (%)	>21 days N=32 (%)	*P*-value*
Age (years)				0.276			0.087			0.128
≤45	106	33 (39.3)	73 (47.1)		81 (48.2)	25 (35.2)		96 (46.4)	10 (31.3)	
>45	133	51 (60.7)	82 (52.9)		87 (51.8)	46 (64.8)		111 (53.6)	22 (68.7)	
Gender				0.226			0.367			
Female	45	12 (14.3)	33 (21.3)		29 (17.3)	16 (22.5)		37 (17.9)	8 (25)	0.337
Male	194	72 (85.7)	122 (78.7)		139 (82.7)	55 (77.5)		170 (82.1)	24 (75)	
Family history				0.165			0.242			0.700
No	224	76 (90.5)	148 (95.5)		155 (92.3)	69 (97.2)		193 (93.2)	31 (96.9)	
Yes	15	8 (9.5)	7 (4.5)		13 (7.7)	2 (2.8)		14 (6.8)	1 (3.1)	
WHO pathology				1.000			1.000			1.000
Type I	0	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Type II/III	239	84 (100)	155 (100)		168 (100)	71 (100)		207 (100)	32 (100)	
T stage[a]				0.140			0.538			0.151
T1–2	72	20 (23.8)	52 (33.5)		53 (31.5)	19 (26.8)		66 (31.9)	6 (18.8)	
T3–4	167	64 (76.2)	103 (66.5)		115 (68.5)	52 (73.2)		141 (68.1)	26 (81.2)	
N stage[a]				0.139			0.558			0.186
N0–1	37	17 (20.2)	20 (12.9)		28 (16.7)	9 (12.7)		35 (16.9)	2 (6.3)	
N2–3	202	67 (79.8)	135 (87.1)		140 (83.3)	62 (87.3)		172 (83.1)	30 (93.7)	
Overall stage[a]				0.763			0.275			0.340
III	129	48 (57.1)	81 (52.3)		92 (54.8)	37 (52.1)		109 (52.7)	20 (62.5)	
IVA–IVB	110	36 (42.9)	74 (47.7)		76 (45.2)	34 (47.9)		98 (47.3)	12 (37.5)	
Cycles of all				0.000			0.002			0.239
3	151	67 (79.8)	84 (54.2)		117 (69.6)	34 (47.9)		134 (64.7)	17 (53.1)	
4–5	88	17 (20.2)	71 (45.8)		51 (30.4)	37 (52.1)		73 (35.3)	15 (46.9)	

Notes: [a]According to the 7th edition of the AJCC/UICC staging system. *Two-sided χ^2 test.
Abbreviations: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control.

C (≤21 vs >21 days). Patient's characteristics by IC-IMRT interval are listed in Table 1. There were more patients receiving three cycles of chemotherapy in the patients with an IC-IMRT interval of ≤7 days in Group A (≤7 vs >7 days) and an IC-IMRT interval of ≤14 days in Group B (≤14 vs >14 days). There were no significant differences in patient characteristics in Group C (≤21 vs >21 days).

The median follow-up time was 40 months (range, 4–58 months). The 3-year OS, DMFS, LRFS, and DFS were 82.7%, 87.5%, 92.5%, and 80.6%, respectively. Thirty patients with details on treatment failure are listed in Table 2. There were less patients with LRFS in the patients with an IC-IMRT interval of ≤7 days in Group A.

Table 3 shows the univariate analyses of survival outcomes. The IC-IMRT interval including Group A, Group B, and Group C was not significantly associated with OS, DMFS, LRFS, or DFS. The multivariate analysis shows that the tumor stage was the independent significant predictor for OS, DMFS, LRFS, and DFS in Table 4. The survival curves of OS and DFS in Group A, Group B, and Group C are shown in

Table 2 Patterns of failure in 239 patients in different groups

Characteristics	N=30	Group A		Group B		Group C	
		≤7 days, n=84 (%)	>7 days, n=155 (%)	≤14 days, n=168 (%)	>14 days, n=71 (%)	≤21 days, n=207 (%)	>21 days, n=32 (%)
Recurrence							
Primary recurrence	12	0 (0.0)	12 (7.7)	4 (2.4)	8 (11.3)	8 (3.9)	4 (12.5)
Nodal recurrence	5	0 (0.0)	5 (3.2)	5 (3.0)	0 (0.0)	5 (2.4)	0 (0.0)
Distant metastasis							
Bone metastasis	3	2 (2.4)	1 (0.6)	2 (1.2)	1 (1.4)	2 (1.0)	1 (3.1)
Lung metastasis	7	3 (3.6)	4 (2.6)	5 (3.0)	2 (2.8)	7 (3.4)	0 (0.0)
Liver metastasis	3	1 (1.2)	2 (1.3)	2 (1.2)	1 (1.4)	3 (1.4)	0 (0.0)
Mediastinal metastasis	1	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)
Axilla	1	0 (0.0)	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)
Multiple metastasis	15	6 (7.1)	9 (5.8)	11 (6.5)	4 (5.6)	11 (5.3)	4 (12.5)

Table 3 Univariate Cox regression analysis of prognostic factors

Characteristics	OS		DMFS		LRFS		DFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Treatment interval								
≤7 vs >7 days	1.410 (0.724–2.746)	0.312	0.917 (0.448–1.875)	0.812	41.421 (0.672–252.5992)	0.077	1.316 (0.702–2.467)	0.391
Treatment interval								
≤14 vs >14 days	1.185 (0.626–2.243)	0.602	1.150 (0.544–2.428)	0.715	2.296 (0.886–5.593)	0.087	1.151 (0.614–2.157)	0.661
Treatment interval								
≤21 vs >21 days	1.316 (0.586–2.658)	0.506	1.598 (0.658–3.884)	0.301	2.146 (0.700–6.584)	0.182	1.283 (0.574–2.869)	0.543
Age (years)								
≤45 vs >45	1.407 (0.758–2.612)	0.279	1.843 (0.872–3.891)	0.109	1.560 (0.577–4.220)	0.381	1.759 (0.949–3.258)	0.073
Gender								
Female vs male	0.839 (0.402–1.749)	0.639	0.637 (0.286–1.418)	0.269	0.965 (0.277–3.360)	0.956	0.828 (0.400–1.717)	0.613
T stage[c]								
T1–2 vs T3–4	2.903 (1.225–6.880)	0.015	3.294 (1.155–9.392)	0.026	3.575 (0.817–15.637)	0.091	3.201 (1.357–7.551)	0.008
N stage[c]								
N0–1 vs N2–3	1.806 (0.645–5.054)	0.260	2.866 (0.685–11.994)	0.149	1.440 (0.329–6.299)	0.628	2.748 (0.853–8.858)	0.090
Overall stage[c]								
III vs IVA–B	5.307 (2.543–11.073)	0.000	4.116 (1.848–9.168)	0.001	10.159 (2.321–44.426)	0.002	5.779 (2.787–11.982)	0.000
Cycles of IC								
1 vs 2–3	0.750 (0.268–2.099)	0.584	0.473 (0.113–1.978)	0.305	2.158 (0.703–6.623)	0.179	0.668 (0.240–1.864)	0.441
Cycles of Con								
1 vs 2–3	1.978 (1.083–3.611)	0.026	1.964 (0.977–3.950)	0.058	1.352 (0.500–3.658)	0.552	1.644 (0.909–2.972)	0.100
Cycles of all								
3 vs 4–5	1.684 (0.926–3.063)	0.088	1.377 (0.685–2.768)	0.370	2.491 (0.948–6.545)	0.064	1.376 (0.768–2.466)	0.283

Abbreviations: Con, concurrent chemotherapy; DFS, disease-free survival; DMFS, distant metastasis-free survival; IC, induction chemotherapy; LRFS, locoregional relapse-free survival; OS, overall survival.

Figure 1. There was no significant difference in OS and DFS among Group A, Group B, and Group C. But, it appears that there was a trend toward improvement in the outcome of ≤7 days group in OS from the Kaplan–Meier curves.

Discussion

Recently, induced chemotherapy has attracted much attention because in recent successful trials it has been found that it can reduce tumor volume and eliminate micrometastasis before

Table 4 Multivariate Cox regression analysis of prognostic factors

Characteristics	OS		DMFS		LRFS		DFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Treatment interval								
≤7 vs >7 days	1.288 (0.602–2.759)	0.514	0.781 (0.330–1.852)	0.575	41.421 (0.672–252.5992)	0.947	1.337 (0.654–2.737)	0.426
Treatment interval								
≤14 vs >14 days	0.744 (0.297–1.860)	0.527	0.788 (0.238–2.607)	0.696	0.883 (0.253–3.088)	0.846	0.880 (0.352–2.197)	0.784
Treatment interval								
≤21 vs >21 days	1.371 (0.470–4.000)	0.564	1.830 (0.506–6.623)	0.357	1.250 (0.298–5.243)	0.760	1.085 (0.372–3.160)	0.882
T stage[c]								
T1–2 vs T3–4	2.643 (1.079–6.475)	0.034	2.865 (0.970–8.461)	0.057	3.490 (0.746–16.323)	0.112	2.998 (1.233–7.290)	0.015
N stage[c]								
N0–1 vs N2–3	3.124 (1.093–8.935)	0.034	4.846 (1.136–20.678)	0.033	2.657 (0.586–12.047)	0.205	5.027 (1.534–16.469)	0.008
Overall stage[c]								
III vs IVA–B	4.994 (2.347–10.627)	0.000	4.156 (1.831–9.430)	0.001	8.793 (1.945–39.742)	0.005	5.756 (2.735–12.116)	0.000
Cycles of all								
3 vs 4–5	1.370 (0.703–2.669)	0.355	1.322 (0.611–2.863)	0.479	1.274 (0.447–3.631)	0.651	1.120 (0.583–2.154)	0.734

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; LRFS, locoregional relapse-free survival; OS, overall survival.

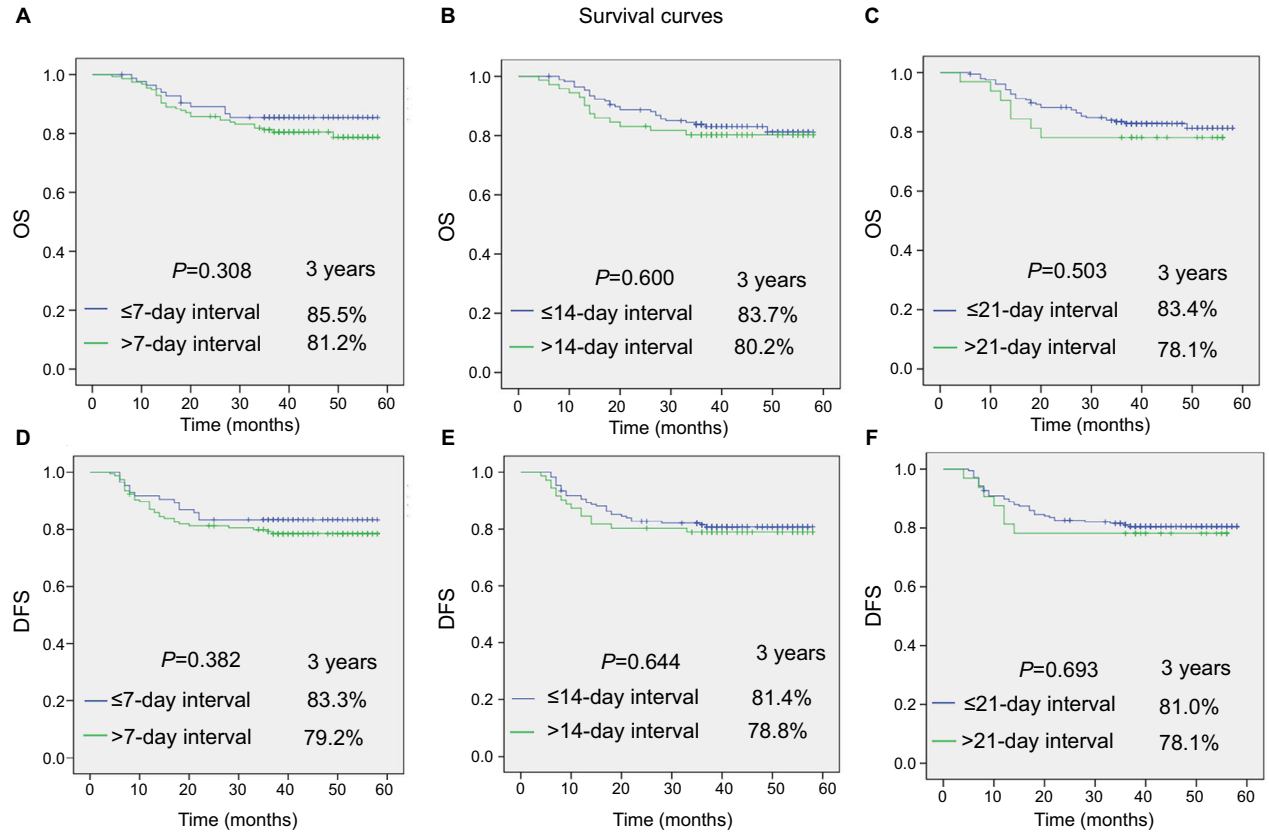

Figure 1 Kaplan–Meier OS (**A**–**C**) and DFS (**D**–**F**) curves for the 239 patients grouped the data by interval.
Note: *P*-values were calculated by the unadjusted log-rank test.
Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; OS, overall survival.

radiotherapy. Following these positive results, IC has become a more promising treatment.[6,12–14] However, no published scientific or clinical data to support an exact time frame between IC and concurrent chemoradiation are available yet. This is the first research to explore the impact of timing between IC and radiotherapy on outcomes in patients with NPC.

Comparison of the results of IT in previous research

Positive results

The IT of adjuvant therapy after surgery has been extensively reported by previous studies. Several retrospective cohort studies have found that a longer IT is associated with poor oncological outcomes for patients with breast, endometrial, head, and neck cancers.[9–11,15] In some studies,[16,17] distant metastasis rates also appeared to increase in women who received radiotherapy for >8 weeks postoperative. In patients with unresected head and neck cancers, delays of 1 month in the initiation of radiotherapy tended to increase the risk of local recurrence at 5 years.[18–20] For head and neck cancers, patients who started radiotherapy >6 weeks after the operation had a higher chance of local recurrence.[21–24] In one study,[25] the 5-year survival rates of patients with non-small-cell lung cancer receiving radiotherapy at 1–6 weeks, 7–8 weeks, and >8 weeks after surgery were 61%, 46%, and 30%, respectively. Recently, a study on 308 endometrial cancer patients found that delay (≥9 weeks) in beginning adjuvant RT after hysterectomy was associated with poor survival outcomes.[26]

Negative results

Interval timing of postoperative radiotherapy after breast-conserving surgery was not significantly associated with time to local recurrence, FFS, or OS in patients receiving adjuvant endocrine therapy for radiotherapy who had a delay of up to about 20 weeks between treatments as found in the study by Clarke et al.[27] In the trial of the International Breast Cancer Research Group, there was no significant correlation with LRFS, DFS, and OS between the timing of radiotherapy after breast-conserving surgery in patients receiving initial or endocrine therapy.[28,29] Two population-based cohort studies also found that starting radiotherapy soon after breast-conserving surgery did not improve long-term survival in patients with or without chemotherapy. The study of He et al[30] showed that the delay in the beginning of IMRT in locally advanced breast cancer did not increase the likelihood of locoregional recurrence, distant metastasis, and death.

Our result

In our current analysis, characteristics in ≤7 and >7 days groups are relatively balanced (Table 1). Although there were more patients receiving three cycles of chemotherapy in the patients with an IC-IMRT interval of ≤7 days in Group A (≤7 vs >7 days), the multivariate analysis shows that the cycles of chemotherapy were not the independent significant predictor for OS, DMFS, LRFS, and DFS (Table 4). Although time interval between IC and definitive RT was not significantly associated with OS, DMFS, LRFS, and DFS, shorter time interval patient groups showed better oncological outcomes. In Figure 1, shorter time interval patient groups showed higher survival curves (OS and DFS) during all time of follow-up duration compared with longer time interval patient groups. Moreover, the survival curves did not cross each other. This phenomenon was particularly evident in Group A (≤7 vs >7 days). It appears that there is a trend toward improvement in the outcome of ≤7 days group in OS and DFS from the Kaplan–Meier curves. In addition, patient group with a time interval of <7 days showed no locoregional recurrences (Table 2).

Thus, we suggested that patients should start IMRT as soon as possible after IC. It is also feasible to postpone radiotherapy for 1–3 weeks if patients were unable to receive radiotherapy immediately due to chemotherapy complications such as bone marrow suppression.

Limitations

The weakness in this study should be acknowledged. First, the data were collected from a single institution. Furthermore, plasma Epstein–Barr virus (EBV) DNA[31–33] was not given consideration since the data of plasma EBV DNA were incomplete. Moreover, median follow-up time was 40 months in this study. The long-term outcome needs a follow-up of >40 months in order to document it in more detail. It is impossible to analyze the impact of an IT of >4 weeks or longer on survival because there were few cases in these patients who had a longer interval.

Conclusion

It is feasible to postpone radiotherapy for 1–3 weeks if patients were unable to receive radiotherapy immediately due to chemotherapy complications such as bone marrow suppression. However, we suggest that patients should start IMRT as soon as possible after IC.

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Disclosure

The authors report no conflicts of interest in this work.

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