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Original Article

Clinical Implication of Simultaneous Intensity-modulated Radiotherapy Boost to Tumor Bed for Cervical Cancer with Full-thickness Stromal Invasion

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Abstract

Objective: The objective of this study was to retrospectively explore the clinical implications of simultaneous intensity-modulated radiotherapy (IMRT) boost to the tumor bed in cervical cancer with full-thickness stromal invasion (FTSI).

Patients and Methods: Patients diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB and IIA cervical cancer with confirmed FTSI were included. Patients received pelvic IMRT from a dose of 50.4 Gy in 28 fractions with (or without) a simultaneous integrated boost (SIB) to 58.8 Gy in 28 fractions for the tumor bed. The progression-free survival (PFS), overall survival (OS), and pelvic-PFS (p-PFS) were analyzed using the Kaplan–Meier method, and independent prognostic factors were explored by Cox regression analyses.

Results: Patients without a tumor bed boost had a poor prognosis. The 5-year OS was 81.3% versus 58.3% and the 5-year PFS rates were 75.0% versus 57.6% (boost vs non-boost). The FIGO stage, pathology, adjuvant chemotherapy, and tumor bed boost were independent factors affecting both the 5-year OS and PFS. Subgroup analysis showed that the SIB group had a higher 5-year OS, PFS, and p-PFS for different stages, lymph node status, and risk groups than the non-SIB group. Recurrence occurred in 268 of 910 (29.5%) patients without SIB and 49 of 293 (16.7%) with SIB. Among patients with recurrence, 113 of 282 (40.1%) in the non-boost group compared with 14 of 51 (23.0%) patients in the boost group had a pelvic recurrence. Tumor bed boost resulted in an increase in the mean radiation dose to the intestine, rectum, and bladder, although there were no differences in the rates of acute and late toxicities between the 2 groups.

Conclusion: Tumor bed boost by external beam radiotherapy (EBRT) is an effective and safe method for patients with FTSI and risk factors. Compared with the standard prophylactic radiation, tumor bed boost by EBRT was not associated with increased acute and late toxicities.

Key words: cervical cancer; intensity-modulated radiotherapy boost; full-thickness stromal invasion; recurrence; survival.

Implications for Practice

This study retrospectively examined prognosis in 1203 patients with FIGO stage IB and IIA squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma of the cervix with full-thickness stromal invasion who underwent standard abdominal radical hysterectomy and pelvic lymph node dissection. We found that a tumor bed boost may improve survival and decrease recurrence, and was not associated with any significant increase in acute and late toxicities. Our study makes a significant contribution to clinical practice because there is currently no standardized treatment for patients with cervical cancer and full-thickness stromal invasion after radical hysterectomy and pelvic lymph node dissection.

Introduction

Cervical cancer is the fourth most common cancer among women worldwide[1,2] and a leading cause of cancer death among women in developing countries.[3,4] With the development of treatment, a 47% reduction in the risk of recurrence has been reported and the curative ratio and survival rate have improved, resulting in a reported 5-year overall survival (OS) of 70%-80%.[5,6] For early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IB-IIA), the reported 5-year OS was over 90%.[7] Radical surgery is typically reserved for most newly diagnosed early-stage patients, such as those with stage IA, IB1, IB2, and some selected IIA1.[8] Adjuvant therapy is recommended in patients with intermediate and/or high-risk

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factors.[9-11] However, despite favorable prognosis in early-stage cervical cancer with a reported 5-year progression-free survival (PFS) and OS of 75%-95%, respectively,[9,12] recurrent rates among patients undergoing radical hysterectomy and pelvic lymphadenectomy are 3%-5%.[13]

In clinical practice, middle or deep one-third of stromal invasion is thought to be an intermediate-risk factor for recurrence, while parametrial involvement has been identified as a high-risk factor for recurrence[14,15]; therefore, adjuvant therapy has been recommended in these patients. Full-thickness stromal invasion (FTSI) lies between microinvasive parametrial involvement and deep stromal invasion (DSI). It is estimated that DSI is of prognostic significance in cases with early-stage cervical cancer after radical treatment, and cases with FTSI had a worse prognosis than those with middle or deep one-third of stromal invasion. Adjuvant radiotherapy (RT) is recommended for patients with parametrial extension, DSI, and positive margins or nodes and significantly improves the PFS and OS. The adjuvant RT dosage normally prescribed is 45-50 Gy, which is a prophylactic dose for tumor recurrence. However, for patients with FTSI, there is limited evidence that the adjuvant dose provides adequate treatment due to the potential for microscopic residual lesions. Therefore, we postulated that an initial pelvic RT dose of 45-50 Gy for the preoperative tumor bed was inadequate. Owing to the postoperative pelvic anatomical position, brachytherapy (BT) boost failed to reach the preoperative tumor bed in these patients.[5] To date, there is no definitive therapy for patients with FTSI and an external beam radiotherapy (EBRT) boost to the tumor bed should be considered as a treatment option.

In this single-institution study, the primary objective was to evaluate the effects of EBRT boost on the tumor bed after radical hysterectomy and pelvic lymphadenectomy for stage IB-IIA with full-thickness stromal invasion. The secondary objective was to determine the risk factors and to evaluate the toxicity of tumor bed boost RT in patients with full-thickness stromal invasion.

Materials and Methods

Patient Selection

A total of 1203 patients with FIGO (2009) stage IB-IIA were involved in the study cohort, and all cases underwent standard abdominal radical hysterectomy and pelvic lymph node dissection (PLND) in the Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center (China) between 2006 and 2014. The inclusion criteria were listed as follows: (1) postoperative pathological diagnosed with squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix; (2) postoperative histological confirmation of full-thickness stromal invasion; (3) no neoadjuvant chemotherapy or radiotherapy; and (4) compliance with routine surveillance. Patients with a history of cancer were excluded from the study. Informed consent was obtained from all the patients. The study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center, Shanghai, China.

Adjuvant Therapy

Adjuvant therapy was administered under the guidance of a treating gynecologist based on the histological results. Patients with intermediate-risk factors meeting with the Sedlis criteria, including tumor diameter, depth of stromal invasion, or lymphovascular space invasion (LVSI), and patients with more than one high-risk factor (including parametrial involvement, positive lymph nodes, or positive surgical margins) were administered adjuvant RT or concurrent chemoradiotherapy. Patients received pelvic intensity-modulated radiotherapy (IMRT) with CT planned. Target delineation was based on the Radiation Therapy Oncology Group Consensus Guideline 2008.[16] The tumor bed boost was referred to as the clinical target volume boost (CTV-Boost) and was defined as the site of the primary cervical tumor, and delineation was performed according to the preoperative magnetic resonance image. The CTV consisted of the preoperative gross tumor (CTV-Boost), common, internal, and external iliac lymph nodes, as well as the presacral space, vaginal apex, and parametria. A manual modification was allowed to ensure that CTV encompassed the preoperative tumor volumes. A 5-7 mm (or institution-specific) margin of CTV expansion was used as the planning target volume (PTV). Around the CTV-Boost, a 10-mm uniform expansion was used as the PTV-Boost. Patients with positive common iliac lymph nodes or para-aortic lymph received an extended-field EBRT (Supplementary Figure 1). Planning was performed using a megavoltage simulator with a photon energy of 6 MV. All patients were treated with a total dose of either 45 Gy in 25 fractions (biologically equivalent dose [BED]: 53.1 Gy) or 50.4 Gy in 28 fractions (BED: 59.5) with (or without) a simultaneous integrated boost (SIB) to 58.8 Gy in 28 fractions (BED: 71.1 Gy) to the tumor bed. For patients with positive surgical margins, additional high-dose-rate intracavitary brachytherapy (3500cGy in 5 fractions) was performed using an after-loaded tandem system. Concurrent cisplatin was delivered weekly, at a dose of 40 mg/m^2. Patients with one or more high-risk factors would receive 4-6 cycles of paclitaxel (135 mg/m^2) and carboplatin (area under curve [AUC] = 5) on day 1.

EBRT plan optimization was accepted when 95% of the PTV volume was covered by the prescribed dose. The specified organs at risk constraints of the critical organs were as follows: maximum spinal cord dose ≤ 45 Gy; maximum bladder dose ≤ 85 Gy; maximum rectum dose ≤ 75 Gy; maximum intestine dose ≤ 60 Gy; maximum bilateral femurs dose ≤ 50 Gy; 50% bilateral kidney volume ≤ 18 Gy; 50% duodenum volume ≤ 40 Gy; and maximum dose ≤ 56 Gy.

Follow-up

This study followed the new Society of Gynecologic Oncology's recommendations for post-treatment surveillance.[17] The recommended surveillance was based on the patient's risk of recurrence and personal preferences. During the follow-up visits, physical examination, Papanicolau smear, routine blood test, and serum tumor markers were performed every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly thereafter. Additional radiographic examinations were advised if a suspected recurrent disease was detected. The National Cancer Institute Common Terminology Criteria toxicity scale (version 2.0) was used to evaluate RT-related complications.

Recurrent disease was defined as a new or progressive lesion at any site (intrapelvic diseases, regional lymph nodes, or distant metastases) confirmed by pathologic and/or radiologic methods during the follow-up visits.

Statistical Analyses

Patient clinicopathological characteristics and recurrent status were compared using the χ^2 test or Fisher's exact test

for frequencies variables. To eliminate bias among the factors, a propensity matching score (PSM) was used to match the 2 groups. The patients in these 2 groups underwent 1:1 matching based on FIGO stage, tumor size, parametrial involvement, surgical margin, nerve involvement, and risk for recurrence. The match tolerance was set at 0.2. The probabilities of the PFS, p-PFS, and OS were estimated using the Kaplan–Meier analysis, and a log-rank test was performed to compare survival curves between 2 groups and check the *P*-value. Univariate and multivariate analyses were used by COX proportional hazards regression to identify independent predictors that affected the OS and PFS over time. Statistical significance was set at $P < .05$. All analyses were performed using SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA).

Results

Patient Clinicopathological Characteristics

Based on the inclusion criteria, a total of 1203 patients with full FTSI were identified as stage IB to IIA, comprising 910 (76%) patients in the non-boost group and 293 (24%) patients in the boost group. The mean age of the eligible patients was 50.5 years (range: 18-76). A total of 1014 (84.3%) patients had squamous carcinoma and 119 (10%) had adenocarcinoma. Nodal status was as follows: 545 (45%) patients were lymph node negative and 658 (55%) were lymph node positive. A total of 319 (27%) patients had stage IB1-2, and 884 (74%) had stage IIA1-2 carcinoma. The tumor size was <4 cm in 490 (41%) patients and ≥ 4 cm in 713 (59%) patients. A total of 517 (43%) patients presented with intermediate-risk factors, and 686 (57%) patients were considered to have high-risk diseases. Only 178 (15%) patients were treated without chemotherapy, while 539 (45%) patients received concurrent diamminedichloro-platinum (DDP) chemotherapy, and 188 (16%) patients received both DDP and adjuvant chemotherapy. Recurrence occurred in 268 of 910 (29.5%) patients without SIB. Among patients with SIB, 49 (16.7%) patients experienced recurrence. The specific recurrence sites are listed in Table 1. Among patients with recurrence, 113 of 282 (40.1%) patients in the non-boost group compared with 14 of 51 (23.0%) patients in the boost group had a pelvic recurrence. The baseline showed that there were more patients with risk factors (tumor size ≥4 cm, stage IIA, parametrial extension, and positive surgical margin) in the boost group than in the non-boost group ($P < .05$). To eliminate the bias between the non-boost and boost groups, the patients underwent 1:1 matching based on the FIGO stage, tumor size, parametrial invasion, surgical margin, nerve invasion, and patient risk. The match tolerance was 0.1, and 262 cases in each group were matched. The characteristics of patients in the 2 groups before and after PSM are summarized in Table 1.

Survival and Prognosis

Survival analysis showed that patients without a tumor bed boost had a poor prognosis. The 5-year OS rates were 81.3% and 58.3% (boost vs non-boost, $P < .05$). The 5-year PFS rates were 75.0% versus 57.6% (boost vs non-boost, $P < .05$; Figure 1A and B). The univariate Cox regression analysis revealed that the FIGO stage, pathology, pelvic lymph node metastasis, parametrial involvement, chemotherapy, LVSI, and tumor bed boost were influencing factors for both the 5-year OS and PFS ($P < .05$). In addition, a tumor size ≥ 4 cm was the risk factors for the 5-year PFS ($P < .05$). Multivariate analysis showed that FIGO stage, pathology, chemotherapy, recurrence risk group, and tumor bed boost were independent influencing factors for both the 5-year OS and PFS ($P < .05$). Tumor bed boost can reduce the risk of death by approximately 75% and the risk of recurrence by approximately 65% ($P < .001$). Patients at stage IIA2 had a higher risk of death for the 5-year OS (hazard ratio [HR] = 2.422, 95 confidence intervals [CI]: 1.088-5.395, $P = .009$) and a higher risk of recurrence (HR = 3.913, 95%CI: 1.452-5.548, $P = .031$) than those at IB1. The risk of death in patients with adenocarcinoma was higher than in patients with squamous carcinoma according to the 5-year OS (HR = 3.442, 95%CI: 2.071-5.721, $P < .001$) and PFS (HR = 3.442, 95%CI: 2.211-5.36, $P < .001$). For patients presenting with high-risk factors, the risk of death was higher (HR = 3.647, 95%CI: 1.35-9.852, $P = .011$) than in patients presenting with intermediate-risk factors whose risk of recurrence was approximately 60% compared with high-risk patients (HR = 1.662, 95%CI: 1.126-2.453, $P = .010$). Furthermore, LVSI was an independent risk factor for the 5-year OS (HR = 1.875, 95%CI: 1.24-2.836, $P = .003$). A tumor size ≥ 4 cm was an independent risk factor for the 5-year PFS, while a tumor size <4 cm reduced the risk of recurrence by approximately 40% (HR = 1.643, 95%CI: 1.092-2.241, $P = .009$; Figure 2A and B).

Subgroup Analyses on the Role of Tumor Bed Boost

The Kaplan–Meier curves showed that the tumor bed boost had a significant effect on the rate of 5-year OS, PFS, and p-PFS in patients with different staging, risk groups and lymphatic status ($P < .05$). Subgroup analysis showed that the tumor bed boost had a high 5-year OS, PFS, and p-PFS at any stage from IB to IIA ($P < .05$; Figure 3). For patients presenting with intermediate risk factors, the 5-year OS was 92.3% versus 76.2% (boost vs non-boost) ($P = .003$). For patients presenting with high-risk factors, the 5-year OS was 75.2% versus 50.8% (boost vs non-boost) ($P < .001$) (Figure 4A and B). The 5-year PFS was 85.2% versus 67.8% (boost vs non-boost) ($P = .002$) among patients presenting with intermediate-risk factors and 68.8% versus 56.3% in patients with high-risk factors ($P < .001$; Figure 4C and D). For patients without positive lymph nodes, the 5-year OS was 93.8% in the boost group compared with 70.2% in the non-boost group ($P < .001$). For patients with positive lymph nodes, the 5-year OS was 75% versus 50% (boost vs non-boost) ($P < .001$) (Figure 5A and B). The 5-year PFS was 86.7% versus 62.5% (boost vs non-boost) ($P < .001$) among patients without lymph node metastasis and 66.7% versus 54.5% in patients with positive lymph nodes (boost vs non-boost) ($P = .001$) (Figure 5C and D). The 5-year p-PFS was 85.5% versus 75.0% (boost vs non-boost) among the entire cohort ($P < .000$; Figure 1C). The p-PFS was 94.5% versus 70.7% (boost vs non-boost, $P = .004$) at stage IB and 81.3% versus 76.1% ($P = .004$) at stage IIA (Figure 3E and F). For patients presenting with intermediate factors, the p-PFS was 92.3% versus 81.4% ($P = .017$). For patients presenting with high-risk factors, the p-PFS was 81.4% versus 71.6% ($P = .004$; Figure 4E and F). For patients without lymph node metastasis, the p-PFS was 91.8% versus 82.2% ($P = .006$). For patients with positive lymph nodes, the p-PFS was 81.8% versus 73.2% ($P = .006$; Figure 5E and F). For patients with a tumor size < 4 cm, the p-PFS was not different between the

Table 1. Clinical and pathologic characteristics for patients with FTSI before and after PSM.

	Before match (n = 1203)		P	After match (n = 524)		P
	Non-boost	Boost		Non-boost	Boost	
Age, years						
<60	738 (81.1%)	236 (80.5%)	.834	213 (81.3%)	211 (80.5%)	.824
≥60	172 (18.9%)	57 (19.5%)		49 (18.7%)	51 (19.5%)	
FIGO stage						
IB_1	171 (18.8%)	29 (9.9%)	.001	29 (11.1%)	29 (11.1%)	.999
IB_2	93 (10.2%)	26 (8.9%)		22 (8.4%)	21 (8.0%)	
IIA_1	291 (32.0%)	94 (32.1%)		88 (33.6%)	89 (34.0%)	
IIA_2	355 (39.0%)	144 (49.1%)		123 (46.9%)	123 (46.9%)	
Pathology						
Squamous	774 (85.1%)	240 (81.9%)	.427	221 (84.4%)	214 (81.7%)	.515
Adenocarcinoma	85 (9.3%)	34 (11.6%)		23 (8.8%)	31 (11.8%)	
Adenosquamous	51 (5.6%)	19 (6.5%)		18 (6.9%)	17 (6.5%)	
Tumor size						
<4 cm	388 (42.7%)	102 (34.7%)	.015	94 (35.9%)	96 (36.6%)	.856
≥4 cm	521 (57.3%)	192 (65.3%)		168 (64.1%)	166 (63.4%)	
Pelvic nodes						
Positive	477 (52.4%)	171 (58.4%)	.076	145 (55.6%)	150 (57.7%)	.623
Negative	433 (47.6%)	122 (41.6%)		116 (44.4%)	110 (42.3%)	
Para-aortic nodes						
Positive	58 (30.4%)	18 (25.7%)	.464	21 (38.9%)	13 (21.3%)	.039
Negative	133 (69.6%)	52 (74.3%)		33 (61.1%)	48 (78.7%)	
Parametrium						
Positive	25 (2.8%)	55 (18.7%)	<.001	23 (8.8%)	23 (8.8%)	.999
Negative	884 (97.2%)	239 (81.3%)		239 (91.2%)	239 (91.2%)	
Surgical margin						
Positive	13 (1.4%)	10 (3.4%)	.031	5 (1.9%)	7 (2.7%)	.559
Negative	897 (98.6%)	283 (96.6%)		257 (98.1%)	255 (97.3%)	
Chemotherapy						
No chemotherapy	138 (15.2%)	40 (13.7%)	.250	42 (16.0%)	37 (14.1%)	.449
DDP	419 (46.0%)	120 (41.0%)		111 (42.4%)	103 (39.3%)	
Adjuvant-chemo	215 (23.6%)	83 (28.3%)		74 (28.2%)	74 (28.2%)	
Both	138 (15.2%)	50 (17.1%)		35 (13.4%)	48 (18.3%)	
LVSI						
Positive	618 (67.9%)	210 (71.7%)	.227	175 (66.8%)	187 (71.4%)	.257
Negative	292 (32.1%)	83 (28.3%)		87 (33.2%)	75 (28.6%)	
Risk for recurrence						
Intermediate	412 (45.3%)	105 (35.8%)	.005	105 (40.1%)	104 (39.7%)	.929
High	498 (54.7%)	188 (64.2%)		157 (59.9%)	158 (60.3%)	
Recurrence site						
Chest	81 (30.2%)	17 (34.7%)	.474	26 (30.2%)	12 (29.3%)	.387
Abdomen	46 (17.2%)	12 (24.5%)		12 (14.0%)	7 (17.1%)	
Pelvic	92 (34.3%)	11 (22.4%)		28 (32.6%)	14 (34.1%)	
Multi and bone	49 (18.3%)	9 (18.4%)		20 (23.3%)	8 (19.5%)	
Pelvic recurrence						
Yes	113 (40.1%)	14 (23.0%)	.018	51 (19.5%)	21 (8.0%)	<.001
No	169 (59.9%)	47 (77.0%)		210 (80.5%)	241 (92.0%)	

FIGO, International Federation of Gynecology and Obstetrics; FTSI, full-thickness stromal invasion; LVSI, lymphovascular space invasion; PSM, propensity matching score.

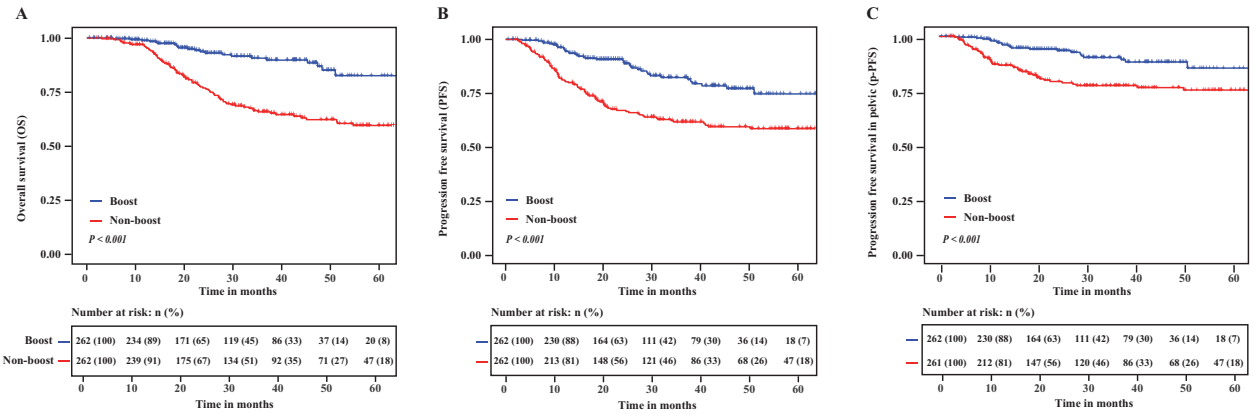

Figure 1. (**A**) Overall survival of boost group and non-boost group, (**B**) progression-free survival (PFS), (**C**) PFS in pelvic; it means the length of time during and after the treatment as long as it does not get worse in pelvic. In a clinical trial, it is one way to see how well the treatment works locally. We called p-PFS.

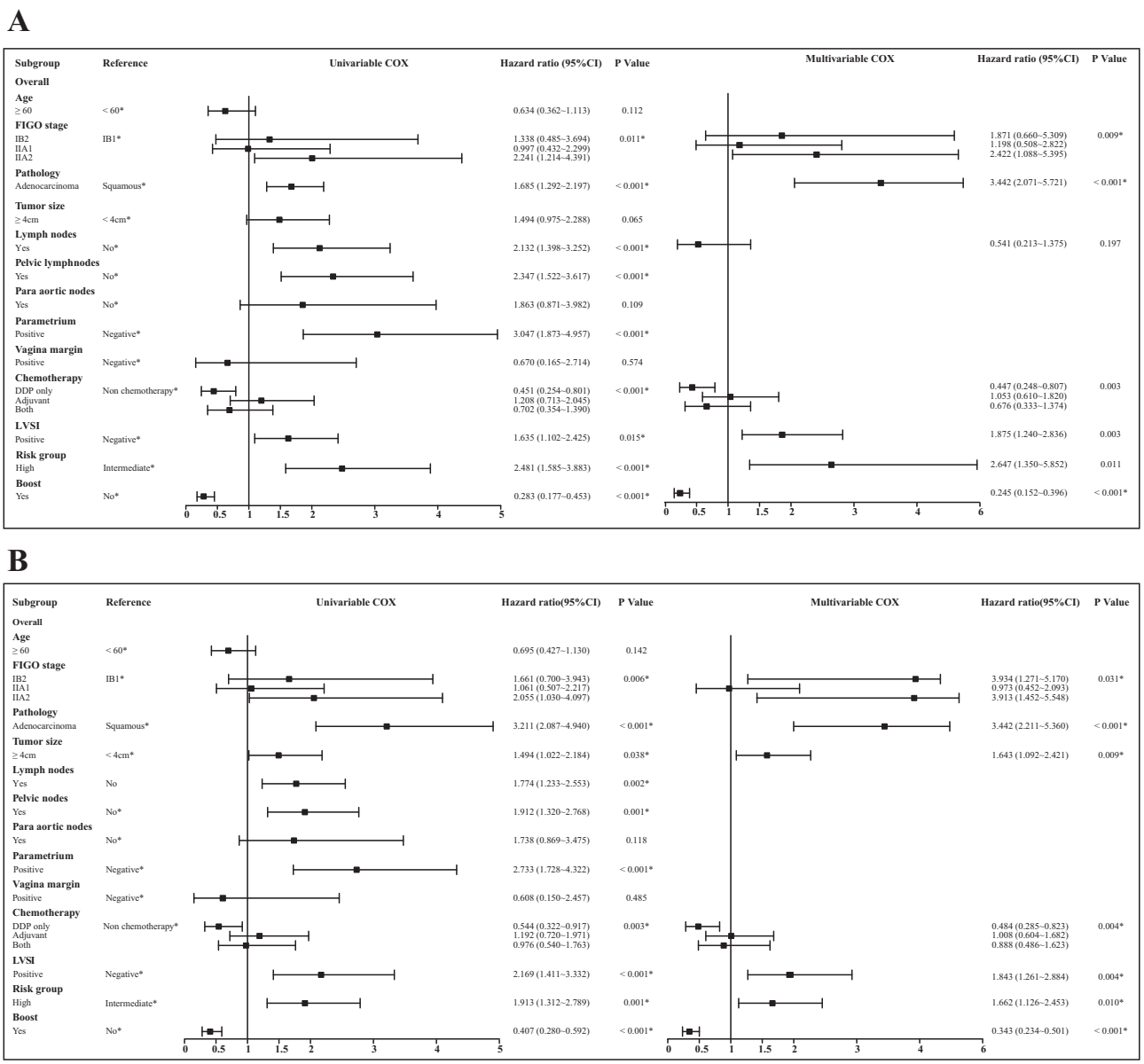

Figure 2. (**A**) The Cox proportional hazards regression analysis for overall survival. (**B**) The Cox proportional hazards regression analysis for progression-free survival. LVSI, lymph-vascular space invasion.

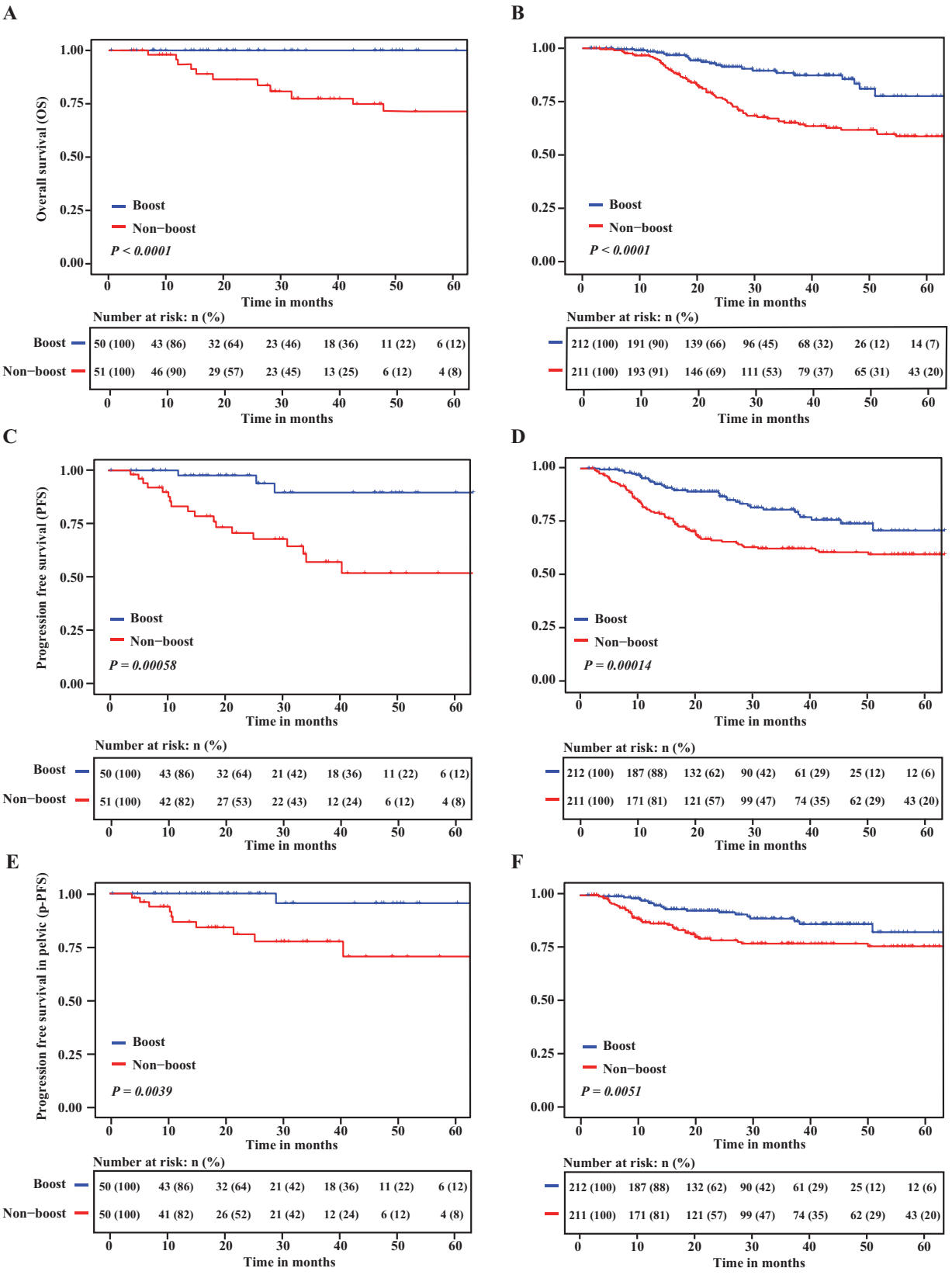

Figure 3. The survival curves for the different stages between the boost group and non-boost group. Overall survival for patients at stage IB (**A**) and IIA (**B**); progression-free survival (PFS) at stage IB (**C**) and (**D**); PFS in pelvic at stage IB (**E**) and (**F**).

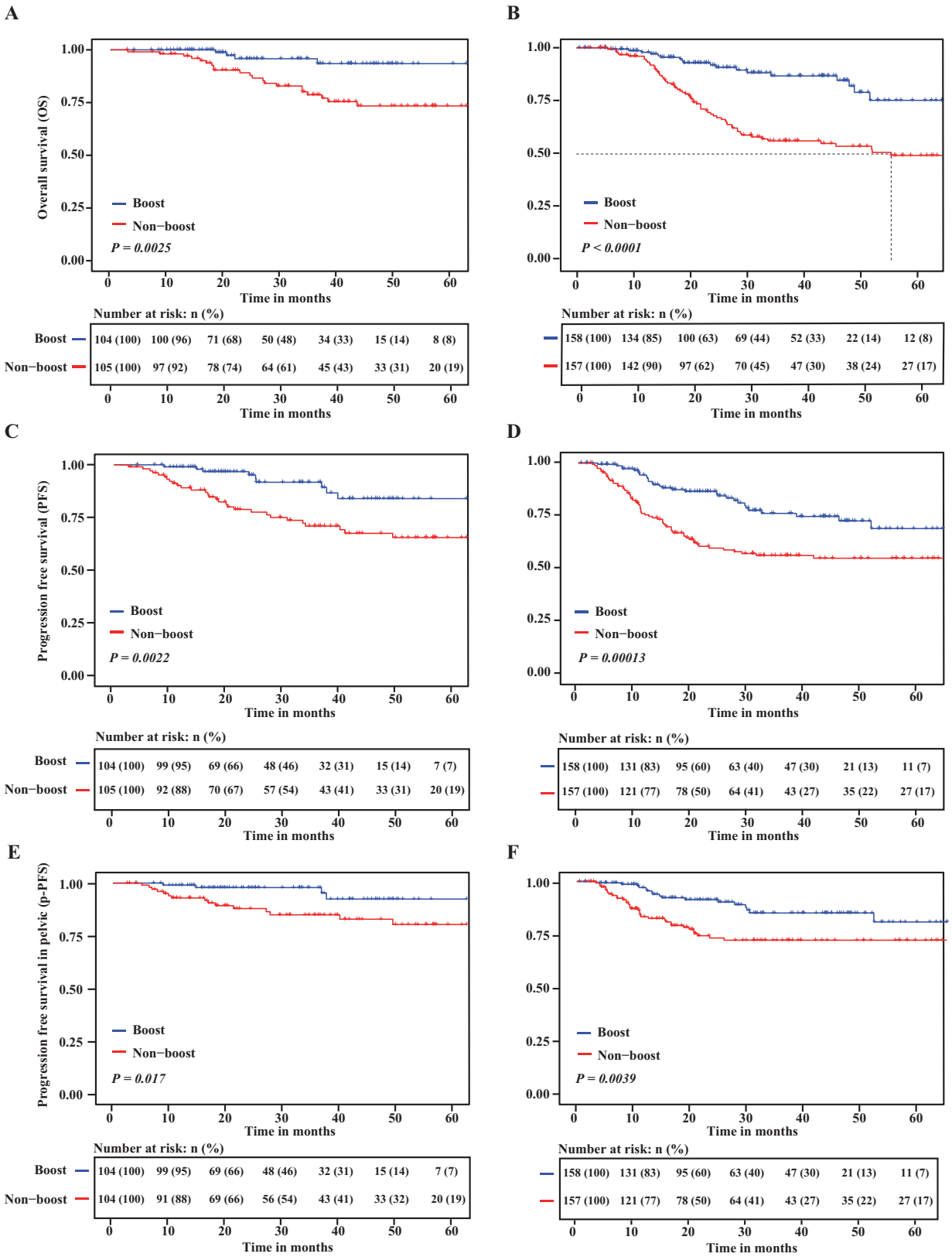

Figure 4. The survival curves for patients with different risk factors between the boost group and non-boost group. Overall survival for patients with intermediate-risk factors IB (**A**) and high-risk factors (**B**); progression-free survival (PFS) for patients with intermediate-risk factors IB (**C**) and high-risk factors (**D**); PFS in pelvic for patients with intermediate-risk factors IB (**E**) and high-risk factors (**F**).

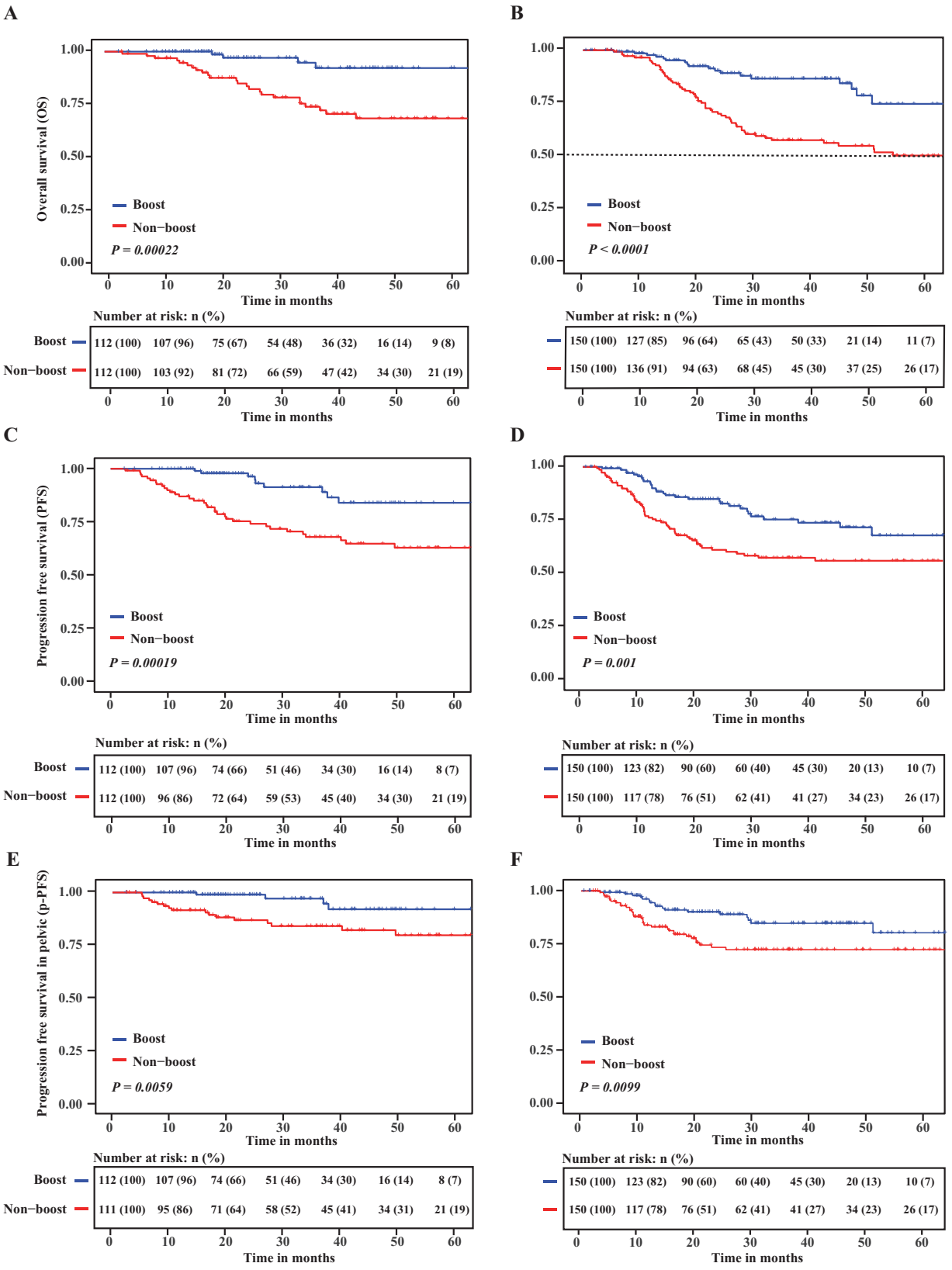

Figure 5. The survival curves for patients with different lymph node statuses between the boost group and non-boost group. Overall survival for patients with negative lymph nodes (**A**) and positive lymph nodes (**B**). Progression-free survival (PFS) for patients with negative lymph nodes (**C**) and positive lymph nodes (**D**). PFS in pelvic for patients with negative lymph nodes (**E**) and positive lymph nodes (**F**).

2 groups. For tumor size ≥ 4 cm, the 5-year p-PFS was 88.2% versus 72.5% ($P < .001$).

Toxicity and Safety Analyses

The use of a tumor bed boost increased the mean radiation dose of the intestine, rectum, and bladder. The mean dose of the normal tissue was 6203cGy versus 5044cGy (bladder: boost vs non-boost), 6193cGy versus 5006cGy (rectum: boost vs non-boost), 5760cGy versus 5039cGy (intestine: boost vs non-boost). Acute effects were observed in the majority of patients. The occurrence rates of grade 1/2 toxicity of the bladder, rectum, and intestine were higher in the boost group than in the non-boost group. However, there was no significant difference in the incidence of grade 1/2 toxicity between the boost and non-boost groups ($P > .05$). The occurrence of grade 3/4 toxicity was lower than that of grade 1/2. Overall, 4/295 (1.2%) patients in the boost group and 7/910 (0.8%) in the non-boost group had grade 3/4 urinary toxicity and 6/295 (1.9%) in the boost group had grade 3/4 rectal toxicity. A comparable number of patients in the boost group had grade 3/4 intestinal toxicity. There was no significant difference in grade 3/4 rectal and intestinal toxicity between the boost and non-boost groups ($P > .05$). The occurrence of late side effects in patients with grade 1/2 toxicity was lower than that of acute effects with no significant differences between the boost and non-boost groups. Only 2/295 (0.8%) patients were reported to have grade 3/4 late rectal side effects (Table 2).

Discussion

Early-stage cervical cancer has a favorable prognosis after radical surgery and adjuvant RT or chemotherapy, although some patients experience recurrence.[18] Our previous study demonstrated that FTSI, which lies between microinvasive parametrial involvement and DSI, is an important prognostic factor in patients with cervical cancer,[12] although there is no standardized management for women with FTSI. We believe that it is important to formulate individualized management for patients with full-thickness stromal invasion without positive parametrial margins.

Although surgery in women with FTSI can result in adequate resection on visual inspection and achieve sufficient resection margins, microscopic residual deposits may remain in the adjacent organs, such as the pelvic organs and the bladder, and these can only be visualized by microscopic examination. Therefore, a dose of 45-50 Gy for the primary tumor bed is inadequate if tumor cells potentially exist. Dosimetric studies have confirmed that brachytherapy is an optimal tool in the context of radiation used to achieve high tumor doses,[19-21] but this was limited by tumor location and radiation distance in patients with a vaginal stump after the radical operation.[22] Brachytherapy dosimetric limitation may expose the tumor to underdosage.[23] Here, we postulate that EBRT as a tumor bed boost may be an effective strategy for patients with FTSI. Moon et al. demonstrated that postoperative RT could improve the prognosis of patients with FIGO stage IB-IIA cervical carcinoma with isolated full-thickness cervical stromal invasion, and found that compared with no adjuvant treatment, postoperative RT could increase DFS and pelvic-failure-free survival.[24] So far, there was no evidence of the effect of the tumor bed boost on the PFS and OS after the surgery.

To the best of our knowledge, this is the first study to evaluate the effects of tumor bed boost on prognosis and toxicity in patients with cervical cancer with FTSI after surgery compared with patients in whom a radiation boost was not administered. Our report showed the benefits of 5-year OS, PFS, and p-PFS from the tumor bed boost. The tumor bed boost significantly improved the OS, PFS, and p-PFS in patients with different stages. A retrospective study of 1240 patients who underwent radical hysterectomy followed by adjuvant treatment within 1-3 different intermediate-risk factors in stage IA/IIB showed that the 5-year OS was 70.6%-89.0% and the PFS was 64.7%-82.8%.[25] Huseyin et al. found that 5-year OS was 82.9% and DFS was 78.2% in patients with early-stage cervical cancer presenting with intermediate-risk factors after surgery and adjuvant RT.[26] In the aforementioned 2 studies, all patients received radiation doses of 45-50.4 Gy with conventional 25-28 fraction. In this study, the patients' OS, PFS, and p-PFS were 92.3%, 85.2%, and 92.3%, respectively, by using an SIB at 59.4 Gy in 28 fractions at the tumor bed. For high-risk patients, the OS, PFS, and p-PFS were 50.8%, 67.8%, and 71.6%, respectively, in the non-boost group. These results were consistent with previously published reports of OS and PFS,[27,28] and were significantly better than the 5-year OS, PFS, and p-PFS of patients without tumor bed boost.

In this study, the site of recurrence was compared between cases with and without the tumor bed boost. Recurrence was identified in 268 (29.5%) in the non-boost group and 49 (16.7%) patients in the boost group. Pelvic recurrence was

Table 2. Mean dose of crucial organs at risk and patients with acute and late toxicity.

Toxicity	Mean dose (cGy)		Grade1/2		*P* value	Grade 3/4		*P* value
	Non-boost	Boost	Non-boost (*n* = 910)	Boost (*n* = 295)		Non-boost (*n* = 910)	Boost (*n* = 295)	
Bladder								
Acute toxicity	5044	6203	376 (43.5%)	158 (53.6%)	.139	7 (0.8%)	4 (1.2%)	.999
Late toxicity			147 (16.2%)	81 (27.4%)	.058	0 (0%)	0 (0%)	-
Rectum								
Acute toxicity	5006	6193	339 (37.2%)	146 (49.6%)	.064	10 (1.1%)	6 (1.9%)	.410
Late toxicity			76 (8.3%)	38 (12.8%)	.249	0 (0%)	2 (0.8%)	-
Gastrointestine								
Acute toxicity	5039	5760	503 (55.3%)	185 (62.6%)	.581	9 (1%)	6 (2.0%)	.505
Late toxicity			102 (11.2%)	48 (16.3%)	.217	0 (0%)	2 (0.8%)	-

observed in 113/910 (12.4%) patients without tumor bed boost and in 14 (5.8%) patients with tumor bed boost. A study found that the incidence of a pelvic sidewall or LN recurrence was high in patients with FTSI who received no adjuvant therapy.[24] We previously demonstrated a strong correlation between full-thickness invasion and large tumor size, which was considered a major risk factor for locoregional relapse, consistent with previous findings.[12,29] Studies have shown that DSI is a strong predictor of pathological parametrial invasion, which could be supported by the theory that cancer cells invade deeply into the cervical stroma and invade parametrial tissue.[30,31] Li et al. reported that the relative risk of recurrence was proportional to the presence of DSI, and that recurrence occurred in almost all patients with FTSI, indicating that women with full thickness were more likely to develop recurrence.[32] These results are of great importance for patients with FTSI, as deep stromal invasion is currently considered an intermediate-risk factor for recurrence, and prophylactic adjuvant RT is not satisfactory. Therefore, we hypothesize that some patients with FTSI were undertreated, explaining the high pelvic recurrence rate. In this setting, our study further confirmed that in all women with FTSI, IMRT boost on the tumor bed achieved good pelvic control.

Theoretically, adding a dose also adds potential adverse effects and toxicities. Our research found that adding a dose to the tumor bed resulted in an increase in the mean dose to the bladder, rectum, and intestine, and an increase in the incidence rates of grade 1/2 gastrointestinal and urinary toxicities. However, this toxicity was not significantly different between the boost and non-boost groups. Moreover, the rates of acute and late toxicities of grade 3/4 were not different between the boost and non-boost groups. Taken together, IMRT boost for the tumor bed is safe and can be applied simultaneously in clinical practice.

The study has several limitations and these results should be interpreted with caution. First, it was a retrospective study, and selection bias and confounding factors were inevitable. Second, nodal metastasis has been revised in the FIGO 2018 staging system, but the majority of the data and references referred to in this study are based on the previous 2009 FIGO staging system. Third, there are few trials on women with cervical cancer due to difficulties in the concept of FTSI and the evaluation of FTSI. The current evidence is limited due to the small number of studies and the power of studies was also limited, and the result of a prospective study by our research group is eagerly awaited.

Conclusion

Compared to the prophylactic dose, the tumor bed boost by EBRT may improve survival and decrease recurrence in women with FTSI and risk factors. Boost on the tumor bed by EBRT was not associated with any significant increase in acute and late toxicity compared with the standard prophylactic dose. EBRT is an effective and safe method for patients with FTSI and risk factors and should be recommended. We await the results of our prospective trials to corroborate these findings.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: Z.Z., J.Z., G.K.; **Provision of study material or patients:** R.B., X.W., J.Z., G.K.; **Collection and/or assembly of data, data analysis and interpretation:** Z.Z., L.J.; **Manuscript writing:** Z.Z., L.J., J.Z., G.K.; **Final approval of manuscript:** All authors.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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