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Stage IB1 cervical cancer treated with modified radical or radical hysterectomy: does size determine risk factors?

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ABSTRACT

Objectives: This study was performed to investigate prognostic factors status at smaller tumors in patients with stage IB1 cervical cancer (CC) who underwent modified radical or radical hysterectomy.

Matherial and metods: Data from patients diagnosed with CC between January 1995 and January 2017 at the Gynecological Oncology Department, Tepecik Training and Research Hospital and Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey, were investigated. A total of 182 stage IB1 CC cases were evaluated retrospectively.

Results: Patients were divided into two groups according to tumor size (< 2 cm and ≥ 2 cm). There were no complications associated with the operation in patients with a tumor size < 2 cm. Among patients with a tumor size ≥ 2 cm, however, 0.9% (n = 1) developed bladder laceration, 0.9% (n = 1) rectum laceration, and 0.9% (n = 1) pulmonary emboli (P = 0.583). The rates of intermediate risk factors (depth of stromal invasion and lymphovascular space invasion) were significantly higher and lymph node involvement significantly more frequent in patients with a tumor size ≥ 2 cm. However, there were no significant differences in parametrial invasion or vaginal margin involvement between the two groups.

Conclusions: Intermediate risk factors and lymph node metastasis were significantly less frequent in patients with small tumors measuring < 2 cm. However, although parametrial involvement and vaginal margin involvement were less common in patients with small tumors compared with large tumors (≥ 2 cm), the differences were not significant.

Key words: cervical cancer; radical hysterectomy; parametrial involvment

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INTRODUCTION

The standard surgical management for International Federation of Gynecology and Obstetrics (FIGO) stage IB1 cervical cancer (CC) is radical hysterectomy and bilateral pelvic lymph node (LN) dissection. CC usually spreads in a lateral direction along the parametrium and vagina, uterine corpus, and LNs via straight local spread or permeation of tumor emboli into the lymphovascular space [1]. Radical resection of the parametrial tissue is the major surgical intervention for CC. The overall survival rate of patients with early stage CC treated by radical hysterectomy is excellent [1]. Parametrectomy is the major reason for postoperative complications, including lower urinary system dysfunction, sexual dysfunction, and anorectal motility disorders, which are attributed to partial denervation of the autonomic nerve supply to the pelvic organs throughout parametrial resection [1–3]. Recent studies have questioned the effectiveness and safety of radical hysterectomy considering the high rate of long-term postoperative complications. To prevent this morbidity, some researchers have attempted to determine methods of preoperatively identifying patients with early stage CC at low risk who may benefit from a less radical procedure without adversely affecting the survival rate.

The FIGO clinical staging system does not include assessment of LN status, microscopic parametrial involvement, vaginal margin involvement, depth of stromal

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invasion (DOI), or lymphovascular space invasion (LVSI) [4–6]. Parametrial involvement, vaginal margin involvement, and LN metastasis are considered high risk factors associated with an increased recurrence rate and decreased survival rate [5]. DOI and LVSI are intermediate risk factors.

Here, we compare the incidences of intermediate and high risk factors in stage IB1 CC patients with small and large tumors (< 2 cm and ≥ 2 cm, respectively). The main purpose of this study was performed to investigate prognostic factors status at smaller tumors in patients with stage IB1 cervical cancer (CC) who underwent modified radical or radical hysterectomy.

MATERIAL AND METHODS

Data from patients diagnosed with CC between January 1995 and January 2017 at the Gynecological Oncology Department, Tepecik Training and Research Hospital and Bakirkoy Dr. Sadi Konuk Training and Research Hospital, were investigated. A total of 182 cases with stage IB1 CC were evaluated retrospectively. All operations were performed by expert gynecological oncologists. The study was approved by the local ethics committees of the participating institutions and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Patients with FIGO stage IB1 CC who underwent radical or modified radical hysterectomy and pelvic ± paraaortic LN dissection were included in the study. Patients with local advanced stage CC and those who had undergone type 1 hysterectomy or surgery without lymphadenectomy were excluded. A flowchart of the recruitment of the study patients is shown in Figure 1. Staging was performed according to the FIGO 2009 clinical staging system by examination under general anesthesia, and patients were evaluated using imaging modalities. The patients completed follow-up evaluations every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually.

Clinical data were obtained from the patients' files. Patient age, menopausal status, type of surgery, adjuvant therapy, disease-free survival, and overall survival were investigated. Surveillance consisted mainly of a physical examination and questioning the patients about their symptoms. Tumor recurrence was confirmed via clinical pelvic exam or imaging studies during a regular visit or following the occurrence of symptoms, such as vaginal spotting or abdominal discomfort. All surgical specimens were evaluated by specialized gynecological pathologists. Tumor size, DOI, LVSI, LN status, vaginal margin status, and parametrial involvement were analyzed in accordance with the pathology reports. The numbers of pelvic and paraaortic LNs and LN involvement were evaluated from the pathology reports. DOI was defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. LVSI was defined as the presence of tumor cells inside the capillary lumens of either the lymphatic or microvascular drainage systems within the primary tumor.

Radical hysterectomy (RH), (type 3 or type C2) consisted of removal of the uterus and adjacent parametrium to its most lateral extent, along the paracolpium and the upper portion of the vagina and the proximal uterosacral ligaments. Modified radical hysterectomy (type 2 or type B) included removal of the uterus, cervix, upper one fourth of the vagina, 1 cm ventral parametrium, 1–1.5 cm lateral parametrium, and 1–2 cm dorsal parametrium. Pelvic lym-

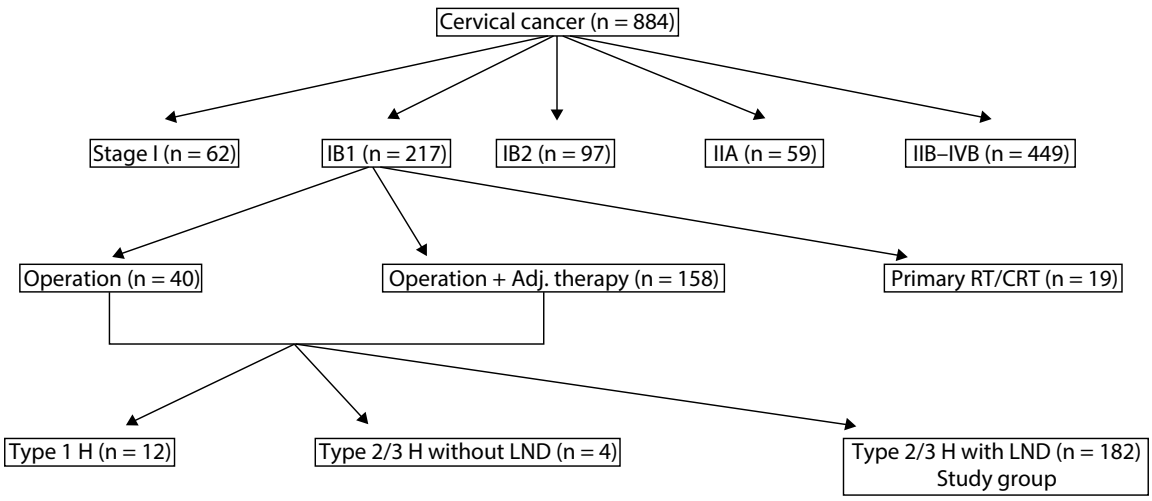

Figure 1. Flowchart of patient recruitment into the study
Adj — adjuvant; RT — radiotherapy; CRT — chemoradiotherapy; H — hysterectomy; LND — lymph node dissection

Table 1. Clinical and demographic patient characteristics

	Tumor size < 2 cm (n = 71)	Tumor size ≥ 2 cm (n = 111)	P
Tumor size, mean ± SD	0.9 ± 0.4	3.0 ± 0.7	< 0.001
Age, mean ± SD	47.0 ± 10.6	48.8 ± 8.9	0.208
Postmenopausal state [%]	36 (50.7)	55 (49.5)	0.879
Hemoglobin, mean ± SD	12.1 ± 1.6	12.3 ± 1.5	0.620
Pelvic LN, mean ± SD	28.0 ± 12.2	26.8 ± 12.1	0.538
Paraaortic LN, mean ± SD	9.4 ± 6.8	10.0 ± 7.2	0.655
Histological type [%] — SCC — AC — ASC	 52 (73.2) 16 (22.5) 3 (4.3)	 82 (73.9) 18 (16.2) 11 (9.9)	0.315
Recurrence [%]	8 (11.3)	8 (7.2)	0.345
DFS, 3 years [%]	91.2	96.2	0.437
DFS, 5 years [%]	89.3	93.5	0.437
OS, 3 years [%]	91.4	93.1	0.720
OS, 5 years [%]	85.5	89.0	0.720

LN — lymph node; SCC — squamous cell carcinoma; AC — adenocarcinoma; ASC —adenosquamous cell carcinoma; DFS — disease free survival; OS — overall survival; SD —standard deviation

Table 2. Treatment options given as primary therapy

	Tumor size < 2 cm (n = 71)	Tumor size ≥ 2 cm (n = 111)	P
Primary therapy [%] — Surgery — Surgery + adjuvant RT — Surgery + adjuvant CRT	 39 (54.9) 19 (26.8) 13 (18.3)	 17 (15.3) 48 (43.2) 46 (41.5)	< 0.001
Surgery type [%] — Type 2 H PPLND — Type 2 H BSO PPLND — Type 3 H PPLND — Type 3 H BSO PPLND	 2 (2.8) 5 (7.0) 6 (8.5) 58 (81.7)	 0 (0) 6 (5.4) 4 (3.6) 101 (91.0)	0.133
IRT, Gy	6–9.25 Gy	5–9.25 Gy	0.758
ERT, Gy	36–54	45–54	0.812
CT [%] — Cisplatin — Cisplatin + Ifosfamide — Carboplatin — Carboplatin + Paclitaxel	 12 (92.4) 0 0 1 (7.6)	 43 (93.7) 2 (4.2) 1 (2.1) 0	0.008

RT — radiotherapy; CRT — chemoradiotherapy; H BSO PPLND — hysterectomy + bilateral salpingo-oophorectomy + pelvic paraaortic lymph node dissection; IRT — internal radiotherapy; ERT — external radiotherapy; CT — chemotherapy

phadenectomy consisted of removal of the lymphatic tissue over the external and common iliac vessels and in the obturator fossa. Paraaortic LN dissection was performed by removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the bifurcation and proceeding to the inferior mesenteric artery if necessary [7]. Pelvic LN dissection was performed all patients. Para-aortic LN dissection was performed in 157 patients (86.3%). The process was applied patients who a bulky LN and/or suspicious appearance in the paraaortic LN area.

Disease-free survival was defined as the interval from the date of primary surgery to detection of recurrence or the latest observation. Overall survival was defined as the interval from the date of primary surgery to death or the latest observation. Survival was analyzed using the Kaplan–Meier method, and the results were compared using the log-rank test. Logistic regression analysis was used to define the predictive factors. The χ^2 test and Student's *t* test were used for unpaired data comparisons. All statistical analyses were performed using MedCalc software (version 14.0 for Windows; MedCalc Software, Mariakerke, Belgium). In all analyses, $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Patients were divided into two groups according to tumor size (< 2 cm and ≥ 2 cm). The clinical and demographic characteristics of the patients are shown in Table 1, and the treatment options used as primary therapy are shown in Table 2. The mean DFS was calculated as 89.2 months (95% CI = 72.4–105.9) for tumors < 2 cm and 78.3 months (95% CI = 67.6–89.1) for ≥ 2 cm tumors in stage IB1 cervical cancer who underwent type B or C2 hysterectomy (P = 0.256). The mean DFS was calculated as 94.3 months (95% CI = 77.7–110.8) for tumors < 2 cm and 79.6 months (95% CI = 68.9–90.3) for ≥ 2 cm tumors (P = 0.124).

Patients with a tumor size < 2 cm did not develop complications from the operation. However, a number of complications were observed in patients with a tumor size ≥ 2 cm, including bladder laceration (0.9%, n = 1), rectum laceration (0.9%, n = 1), and pulmonary emboli (0.9%, n = 1) ($P = 0.583$). In patients with tumors < 2 cm, recurrence was noted in the vagina (5.6%, n = 4), vertebrae (2.8%, n = 2), pelvic region (1.4%, n = 1), and multiple organs (1.4%, n = 1). Patients with tumors ≥ 2 cm showed multiple organ metastases (2.7%, n = 3) and recurrence in the vagina (1.8%, n = 2), pulmonary system (0.9%, n = 1), liver (0.9%, n = 1), and pelvis (0.9%, n = 1).

Patients with tumors < 2 cm and those with tumors ≥ 2 cm were compared according to the presence of intermediate and high risk factors (Tab. 3). The rates of intermediate risk factors were significantly higher in patients with a tumor size ≥ 2 cm compared with < 2 cm. LN involvement was significantly more frequent in patients with tumors ≥ 2 cm, but there were no significant differences in parametrial invasion or vaginal margin involvement between the two

Table 3. Risk factors according to tumor size

		Tumor size < 2 cm (n = 71)	Tumor size ≥ 2 cm (n = 111)	P
Intermediate risk factors	DOI, deep 1/2 [%]	25 (35.2)	58 (52.3)	0.024
	LVSI [%]	17 (23.9)	46 (41.4)	0.016
High risk factors	LN involvement [%]	7 (9.9)	26 (23.4)	0.021
	PI [%]	2 (2.8)	6 (5.4)	0.406
	VM involvement [%]	2 (2.8)	7 (6.3)	0.290

DOI — depth of stromal invasion; LVSI — lymphovascular space invasion; LN — lymph node; PI Ïparametrial invasion; VM — vaginal margin

groups. The other risk factor is histological type that is not in the table. Nineteen (26.8%) of the patients with small tumors (< 2 cm) had histological type of non-squamous cell carcinoma. Similarly, twenty-nine (26.1%) of patients with large tumors (≥ 2 cm) had non-squamous cell carcinoma. No significant difference was found (P = 0.925).

LN involvement was higher in patients with large tumors. Pelvic lymph node involvement was found in 7 (9.9%) patients with small tumors and in 26 (23.4%) of patients with large tumors (P = 0.021). However, the number of patients with paraartic lymph node metastases was very low [2 (1.8%) patients in large tumors, 0 patients in small tumors; P = 0.283].

Subgroup analysis was performed according to patients with a tumor size < 2 cm, DOI < 1/2 (< 5 mm), and LVSI negativity (n = 33) versus patients with a tumor size ≥ 2 cm or presence of any intermediate risk factors independent of tumor size (n = 149). Patients with no intermediate risk factors with a tumor size < 2 cm had lower rates of LN involvement than did patients with a tumor size ≥ 2 cm or presence of any intermediate risk factors (3.0% vs. 21.5%, respectively; *P* = 0.013). However, there were no significant differences in parametrial involvement (3.0% vs. 4.7%, respectively; *P* = 0.672) or vaginal margin involvement (3.0% vs. 5.4%, respectively; *P* = 0.575).

DISCUSSION

This study was performed to compare the incidences of intermediate and high risk factors in stage IB1 CC patients with a small versus large tumor size (< 2 cm vs. ≥ 2 cm). Although type III and type C RH have been shown to have excellent prognoses in terms of survival, the significant morbidity related to the procedure adversely affects patients' quality of life. Therefore, there is growing interest in the use of less radical surgical procedures to replace type III and type C RH [1].

LVSI involvement [8, 9], DOI > 1/2 [8, 10], parametrial microinvasion [1, 8, 11–13], LN metastasis [8, 10, 12], and vaginal margin involvement [12] are significantly more frequent in stage IB1 CC patients with a tumor diameter ≥ 2 cm than in those with smaller tumors. Although parametrial invasion [10] and positive vaginal margin involvement [5, 8, 10] were more frequently associated with tumors ≥ 2 cm in diameter, some studies indicated no significant differences according to tumor size. Studies evaluating microinvasion observed during radical resection of the parametrium, which is the primary aim of radical surgery, showed that tumor size was an independent predictor of parametrial spread according to regression analyses [1, 3, 14]. In our study, parametrial invasion was only detected in eight patients. We found less parametrial invasion in patients with small tumors, but there was no significant difference between the two groups. This may have been because the incidence of parametrial invasion in our group was lower than that in other studies. The rates of intermediate risk factors and LN involvement were significantly lower in patients with small tumors (< 2 cm) compared with large tumors (≥ 2 cm). Consistent with the literature, although vaginal margin involvement was found more frequently in patients with large tumors in the present study, this difference was not significant.

There have been a number of recent reports regarding the application of more conservative surgical procedures in place of radical hysterectomy, which negatively affects quality of life, without increasing the risk of recurrence. The primary aim of avoiding radical surgery is to prevent complications, such as ureteric injury, fistulas, blood loss, and urinary dysfunction. In our cohort, the rates of LN metastasis, parametrial involvement, and vaginal margin involvement were all approximately 3.0% in patients with small tumors who did not have any of the intermediate risk factors evaluated. Patients with a low risk of parametrial spread or disease recurrence may be candidates for less radical surgical procedures. In comparison with CC without parametrial involvement, patients with parametrial involvement had larger tumors (*P* < 0.04), higher incidence of LVSI (*P* < 0.001), greater depth of invasion (*P* < 0.001), and greater rate of pelvic LN metastases (*P* < 0.001) [15]. To detect parametrial spread, it may be possible to investigate factors such as tumor size, DOI, and LVSI, because these factors can be evaluated preoperatively by pathological examination of conization specimens. It is important to identify appropriate candidates and manage them in a suitable way. One of the most important factors responsible for recurrence is tumor size. Tumors ≥ 2 cm in size have an elevated risk of recurrence compared with tumors < 2 cm in size (12.5% vs. 1.2%) [16].

Less radical operations, such as type I hysterectomy with LN dissection, may be viable alternatives for low-risk candidates with clinical factors such as small tumor size, negative LN, superficial invasion, and negative LVSI. It is important to note that even with conservative management, all patients should routinely undergo sentinel node identification or complete pelvic lymphadenectomy [17]. Additional prospective studies are needed to determine whether patients with stage IB1 lesions can be treated with less radical surgical procedures.

This study had several limitations. First, it was a retrospective analysis of patients from various institutions. Due to the retrospective nature of the study, the presence of other potentially confounding variables, such as selection and recall bias, that may have affected our results, could not be excluded. Second, the procedures were performed by many different surgeons (gynecological oncologists). Third, all surgical specimens were evaluated by many different gynecological pathologists. In addition, there was no standardized pathological slide review. Despite these limitations, the similarities in the demographic characteristics of the study population and analysis by expert pathologists increased the validity of our results and mitigated these weaknesses. Moreover, the availability of abundant follow-up data increased the validity of the results.

In conclusion, intermediate risk factors and LN metastasis were found to be significantly less frequent in patients with a small tumor size. Although the rates of parametrial involvement and vaginal margin involvement were lower in patients with small tumors than in those with large tumors, the differences were not significant. Although the results were not highly reliable because of the small number of patients included in our study, the surgical procedure was individualized in patients with small tumors who had a negative LVSI and superficial DOI according to the preoperative pathology reports.

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Conflict of interest

None.

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