

Genital organ involvement in female patients with bladder cancer: evaluation of radical cystectomy specimens

Mesane kanserli kadın hastalarda genital organ tutulumu: Radikal sistektomi örneklerinin incelenmesi

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Abstract

Objective: Radical cystectomy is the gold standard in the treatment of invasive bladder cancer. In female patients, anterior exenteration with cystectomy is the routine treatment procedure. In this study, pathologic specimens of female patients who underwent radical cystectomy with anterior exenteration due to bladder cancer were evaluated to define the rate of genital organ involvement.

Materials and methods: We retrospectively reviewed the records of 16 female patients who underwent radical cystectomy between July 1996 and July 2008 with regard to pathological results for genital organ involvement and concomitant primary cancers of these organs.

Results: Transurethral resection of bladder tumor, showed that 4 patients had pT1 and 12 patients had pT2 tumors. Pathologic evaluation following radical cystectomy revealed that 1 patient had pT0, 3 patients had pT2, 9 patients had pT3, and 3 patients had pT4 tumors. Three patients (18.7%) had genital organ involvement. Statistical analysis showed that the most important variable for genital organ invasion was bladder neck involvement ($p=0.003$).

Conclusion: In women who are candidates for genital organ-sparing cystectomy, surgical intervention has to be individualized. Routine preoperative evaluations should include a thorough genital organ examination, imaging, and whenever needed, vaginal smear and biopsies.

Key words: Cystectomy; urinary bladder neoplasms; uterus; vagina.

Özet

Amaç: Radikal sistektomi invaziv mesane kanserinin tedavisinde altın standarttır. Kadın hastalarda sistektomi ile birlikte ön ekzenterasyon alışlagelmiş uygulamadır. Bu çalışmada mesane kanseri nedeniyle radikal sistektomi ile birlikte ön ekzenterasyon yapılan kadın hastaların patoloji örnekleri değerlendirilerek mesane kanserinde genital organ tutulum oranı belirlenmiştir.

Gereç ve yöntem: Temmuz 1996 ve Temmuz 2008 tarihleri arasında radikal sistektomi yapılan 16 kadın hastanın patoloji sonuçları, genital organ tutulumu ve bu organların aynı anda eşlik eden birincil kanserleri açısından retrospektif olarak incelendi.

Bulgular: Mesane tümörünün transüretral rezeksiyon sonuçlarına göre 4 hastada pT1 ve 12 hastada pT2 tümör saptandı. Radikal sistektomi sonrası patolojik değerlendirmede 1 hastada pT0, 3 hastada pT2, 9 hastada pT3 ve 3 hastada pT4 tümör rapor edildi. Hastalardan 3 tanesinde (%18.7) genital organ tutulumu mevcuttu. İstatistiksel analiz sonucunda, genital organ tutulumu açısından en önemli değişkenin mesane boynu tutulumu olduğu görülmüştür ($p=0.003$).

Sonuç: Genital organ koruyucu radikal sistektomiye aday mesane kanserli kadınlarda cerrahi müdahale seçimi hastaya göre yapılmalıdır. Rutin preoperatif değerlendirme; ayrıntılı genital organ muayenesi, görüntüleme ve gerektiğinde vajinal smear ve biyopsileri de kapsamalıdır.

Anahtar sözcükler: Mesane neoplazmları; sistektomi; uterus; vajina.

The main goals in the treatment of invasive bladder cancer are eradication of cancer, providing high quality of life, and avoiding morbidity and dysfunction due to radical surgery. Although radical cystectomy is the gold standard in the treatment of invasive bladder cancer, particularly in women who undergo anterior exenteration with cystectomy as a result of invasive bladder cancer, surgical technique needs a revision in the orthotopic diversion era.

During anterior exenteration; uterus, fallopian tubes, ovaries, and the proximal third of anterior vagina are resected together with bladder and urethra.^[1] However orthotopic diversion can be performed in women with urethral and anterior vaginal wall preservation.^[2-4] Additional reasons to preserve female genital organs include maintenance of fertility and sexual life, especially in young females.

Pathologic reviews of internal genitalia after anterior exenteration for bladder cancer in women have revealed that genital organs could be preserved during orthotopic diversion; and patients might be spared from adverse effects such as acute early menopause, infertility, and cessation of sexual activity using this approach.^[5,6] It is mandatory to determine the pathologic status of genital organs in patients who are candidates for genital organ-sparing surgery before cystectomy. Yet there have not been sufficient studies to determine which patients may benefit from this approach.

In this study, we evaluated pathologic specimens of patients who underwent radical cystectomy with anterior exenteration due to invasive bladder cancer and report the genital organ involvement rate with bladder cancer. We also described the predictive variables for invasion and coexistence of other tumors in these organs that were confirmed by pathologic evaluation, and discussed the conditions of genital organ-sparing surgery with radical cystectomy.

Materials and methods

Between July 1996 and July 2008 radical cystectomy, anterior exenteration, and urinary diversion was performed in 25 female patients because of bladder cancer at Okmeydanı Training and Research Hospital, Second Urology Clinic. Indications for surgery included high-grade bladder cancer resistant to intravesical treatment and muscle invasive bladder cancer. Nine patients were excluded from the study-3 with a history of previous hysterectomy and bilateral salpingo-oophorectomy for benign causes, 2 with

an orthotopic neobladder urinary diversion without urethrectomy and vaginal wall excision, and 4 with non-transitional cell cancers (2 carcinosarcoma, 2 squamous cell carcinoma)-as the aim of the study was to determine the status of all genital organs in patients with transitional cell carcinoma (TCC).

Transurethral resection of bladder tumor (TUR-BT) was performed for primary diagnosis in each patient. Prior to radical surgery, all patients were evaluated with abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), chest radiography, bimanual examination under general/spinal anesthesia, and bone scan whenever needed for clinical staging. Uterus, fallopian tubes, ovaries, and the proximal third of the vagina and bladder were removed en bloc during radical cystectomy, and bilateral pelvic lymph node dissection was performed in all patients. Either ileal conduit or ureterocutaneostomy was chosen for urinary diversion. None of the patients received neoadjuvant chemotherapy or radiotherapy. Adjuvant chemotherapy was administered in accordance with the final pathological stage.

All extracted organs were evaluated by single pathologist, and step section method was performed on all specimens. Bladder cancer or genital organ based cancer were noted according to the pathological report. Tumors were classified in accordance with the TNM staging system. Clinical and pathological data were collected from the hospital records.

Univariate analysis of contingency tables using chi-square tests was performed to assess the correlation between female internal genitalia involvement and several preoperative and postoperative variables. Exact methods were used to determine statistical significance when small numbers were encountered in the contingency tables (i.e., expected value of any cell is less than five). SPSS 13.0 for Windows package was used in all statistical analysis.

Results

A total of 16 patients were included in the study; median patient age was 73 (range 58-81) years. Ileal conduit was performed in 14 patients and ureterocutaneostomy in 2 patients, together with radical cystectomy, anterior vaginal exenteration, and bilateral pelvic lymph node dissection. Clinical examination combined with TUR-BT pathology determined that 3 patients had cT1 tumors, 9 patients

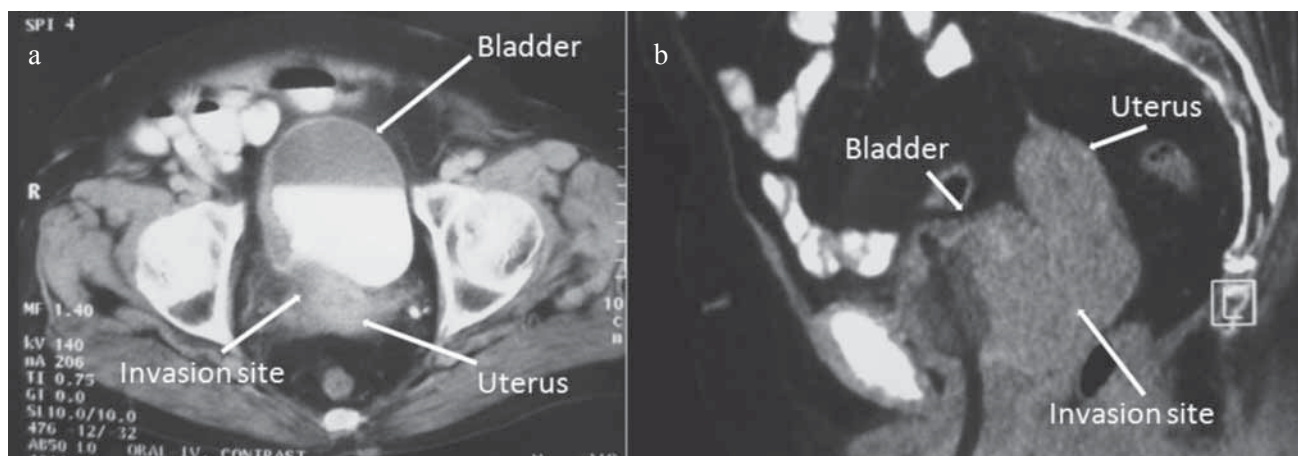


Figure 1 CT scans (a, b) showing invasion of bladder tumor to the uterus.

had cT2, and 4 had >cT2 (3 had signs of genital organ involvement on positive bimanual exam and radiologic findings) disease prior to radical surgery. Fig. 1 shows CT scan images of a posterolaterally located bladder tumor that invades the uterus. All tumors were high grade, and 2 patients had concomitant carcinoma in situ (CIS).

Histological presentation of radical cystectomy specimens was similar to TUR-BT as TCC in 16 patients. The final pathologic stages of patients were pT0 in 1 patient, pT2 in 3 patients, pT3 in 9 patients, and pT4 in 3 patients; 6 had concomitant CIS. A total of 5 patients had lymph node metastasis, 2 had bladder neck involvement, and 1 had urethral involvement according to pathologic evaluation. Of the 16 patients, 3 (18.7%) had genital organ involvement. Examination of specimens was consistent with genital organ-based cancers; cervix cancer was observed in one patient with pT3 high-grade bladder cancer; and in situ vaginal cancer was observed in one patient who had pT2 high-grade bladder cancer (Table 1). Preoperative evaluation of these 2 patients did not yield any sign of secondary cancer, but 3 patients who demonstrated genital

organ involvement with TCC had positive findings at preoperative evaluation according to physical examination and radiologic imaging studies.

Statistical analyses showed that bladder neck involvement was a significant variable for genital organ involvement ($p=0.003$); but TUR-BT stage (superficial/invasive) ($p=0.42$), presence of CIS in TUR-BT specimen ($p=0.658$) or in cystectomy specimen ($p=0.594$), lymph node involvement ($p=0.569$), and urethral involvement ($p=0.087$) were not statistically significant.

On follow-up we could obtain the records of only 9 patients. Mean follow-up was 30.8 months. These records showed that 6 patients had died. Mean time to death was 14.3 (5-40) months. Pathologic results of these 6 patients were pT2 in 1, pT3 in 3, and pT4 in 2 patients (these 2 patients had genital organ involvement). Table 2 summarizes pathologic status and follow-up results of these patients.

Discussion

The routine procedure during radical cystectomy in the female comprises extraction of all genital organs

Table 1. Pathology results after radical surgery of 16 patients with transitional cell carcinoma

Stage	CIS (+)	Lymph node involvement	Bladder neck involvement	Urethral involvement	Genital organ involvement	Secondary cancer in genital organs
pT0 (n=1)	1	0	0	0	0	-
pT2 (n=3)	2	1	0	0	0	1 (in situ vaginal cell cancer)
pT3 (n=9)	1	2	0	0	0	1 (cervix cancer)
pT4 (n=3)	2	2	2	1	3	-

CIS: Carcinoma in situ.

Table 2. Summary of follow-up results in 9 patients

Patient number	Cystectomy pathology	Invaded/dissected lymph node (involved/extracted)	Death (cause of death)	Time of follow-up or death (months)	Genital organ involvement (-/+)	Adjuvant chemotherapy
1	pT2	(+) 2/27	Yes (metastasis of tumor)	8	(-)	Received
2	pT2	(-) 0/12	No	73	(-)	Not received
3	pT3	(-) 0/32	No	72	(-)	Not received
4	pT3		Yes (myocardial infarction)	10	(-)	Not received
5	pT3	(+) 5/28	Yes (uretero-ileal anastomosis leakage+peritonitis)	5	(-)	Received
6	pT3	(+) 7/7	Yes (chronic renal failure diagnosed before surgery)	10	(-)	Received
7	pT4	(+) 8/8	Yes (metastasis of tumor)	40	(+) (vagina)	Received
8	pT4	(+) 15/21	Yes (metastasis of tumor)	13	(+) (uterus, cervix and parametrium)	Received
9	pT4	(-) 0/13	No	20	(+) (uterus)	Received

in addition to the bladder. It is a convenience for the surgeon that this population is mostly composed of rather elderly postmenopausal patients without an expectation of future childbearing. Orthotopic urinary diversions have been utilized for females with successful outcomes.^[2] Chang et al.^[7] showed that, in 25 female patients without widespread CIS and bladder neck or trigone involvement, anterior vaginal wall preservation in radical cystectomy with orthotopic neobladder substitution was technically feasible, maintained vaginal length and support, had an acceptable complication rate, and achieved negative margins. This is an important comment to which our study is in accordance with, that bladder neck involvement is an important factor for genital organ involvement particularly for vagina. These findings confirm that in patients with bladder neck involvement, vaginal resection has to be performed due to concerns for cancer control. A different study showed that patients with vaginal resection and ileal conduit diversion reported impeded sexual activity postoperatively.^[8] The debate is ongoing in the literature between cancer control and preservation of functionality. In our study, we were not able to comment on sexual functionality outcomes, since the study population was composed of elderly patients and the number of cases was rather small; nevertheless vaginal involvement was stipulated prior to surgery with the combination of physical examination and

radiologic evaluation in patients who had pT4 cancer according to cystectomy specimens. Candidates for vaginal wall preservation require complete evaluation with physical examination and imaging modalities to expose involvement of vagina. On the other hand, there is a risk for secondary cancer of vagina, as we observed in our study. One pT2 bladder cancer patient without clinical findings for vaginal cancer before radical surgery had in situ vaginal cell cancer. In an effort to avoid these uncommon situations, random vaginal mucosal biopsies before radical surgery might be performed in patients who are candidates for vaginal wall preservation.

In functional aspect, existence of cervix and uterus is not an obligation to support the neobladder posteriorly as reported by Nagele et al.^[9] In our study we encountered uterine invasion in one patient and cervical and uterine invasion in another patient that was anticipated preoperatively. However, one patient with pT3 bladder cancer without genital organ involvement had in situ cervix cancer; this patient was a 68-year-old postmenopausal woman, and there was no need to preserve genital organs. In young patients, childbearing is another concern; achieving pregnancy is possible with an intact genital system. Kennedy et al.^[10] reported a pregnancy after orthotopic continent urinary diversion; in young females who are candidates for genital organ-sparing surgery, performing a smear test may be helpful for excluding cervical cancer which has high incidence.

Another issue is acute early menopause and loss of reproductive ability because of extraction of ovaries in young females. However, protection against acute early menopause can be achieved with hormonal replacement after surgery, and freezing of oocytes can be helpful in avoiding infertility. In our study, none of the patients had ovarian involvement. This data is in accordance with similar studies in the literature.^[5,6] According to our results, ovaries are less likely prone to invasion of bladder cancer than the vagina, uterus, or cervix, and should be preserved in special conditions.

Reliability of genital-organ-sparing cystectomy is a debatable issue considering the collected data in literature. However patients' desire is changing, and quality of life, as well as eradication of cancer, is an important concern after radical cystectomy. Lack of prospective studies and well-established guidelines require the surgeon to make a decision about preserving genital organs. Our final conclusion on the matter is not to protect genital organs in elderly patients with advanced cancer; we routinely perform anterior exenteration because of the high incidence of genital organ invasion and other primary malignancies of genital organs like carcinoma of cervix. However, if genital organ preservation is a necessity, surgical intervention has to be individualized. Routine preoperative evaluations in women with bladder cancer who are candidates for radical cystectomy should be broadened and must include a thorough genital organ examination, imaging, smear, and biopsies whenever necessary.

This retrospective study is composed of a small group of elderly postmenopausal women. As a result, one should be cautious in drawing conclusions about functional outcomes of the procedure like childbearing, acute early menopause, and sexual activity. Nevertheless we can state a prognostic factor, bladder neck involvement, for invasion of genital organs with TCC in accordance with literature and also describe concomitant primary malignancies of genital organs that may change the outcomes of surgery. To clarify the controversies, prospective

randomized studies with larger sample size are needed.

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