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Pelvic Exenteration: Impact of age on surgical and oncologic outcomes

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Abstract

Objective—To evaluate whether preoperative age impacts surgical outcomes, complication rates, and/or recurrence in women undergoing pelvic exenteration.

Methods—All women who underwent a pelvic exenteration for any gynecologic indication at our institution from 1993 to 2010 were included. Women were stratified into groups based on age in years (young: 50, middle: 51–64, and senior: 65). Baseline characteristics, surgical outcomes, early (<60 days) and late (≥ 60 days) postoperative complications, and recurrence/survival outcomes were ascertained. Fisher's exact test or Kruskal-Wallis test was performed. Kaplan-Meier survival curves were compared.

Results—161 patients were included (58 young, 62 in the middle, and 41 senior). Women in the young group predominately had a diagnosis of cervical cancer (82.8%) while women in the senior group primarily had a diagnosis of vulvar or vaginal cancer (70.7%). Senior women were also more likely to have hypertension ($p < 0.0001$) and pulmonary disease ($p = 0.040$). Operative time was significantly shorter for women in the senior group (8.5 hours) compared with the middle (9.5 hours) and young group (10.1 hours) ($p = 0.0089$). There were no significant differences in early or late complications when stratified by age. The overall survival did not differ between age groups ($p = 0.3760$).

Conclusion—Although hypertension and pulmonary disease were more frequent in the senior age group, duration of surgery, blood loss, length of hospital stay and complication rates did not increase with age. Advanced chronological age should not be considered a contraindication to a potentially curative surgical procedure.

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Conflict of interest statement

The authors declare there are no disclosures or conflicts of interest.

Introduction

Over the next four decades, the number of Americans aged 65 years and older is projected to more than double from 40.2 million in 2010 to 88.5 million by 2050 [1]. Thus, an increasing proportion of gynecologic cancer patients will be elderly with primary or recurrent cancer. In a select group of patients with a central recurrence, pelvic exenteration is often the only viable option for cure despite advances in radiation and chemotherapy. Historically, advanced age has been considered a relative contraindication to pelvic exenteration due to the complexity and significant morbidity of the procedure as well as an increase in chronic medical conditions that are found in older patients. Published data demonstrates that carefully selected elderly patients with gynecologic cancers may receive definitive treatment without significant associated morbidity or mortality [2, 3]. Furthermore, studies have also demonstrated that other types of radical surgery, for example, in ovarian cancer debulking can prolong overall survival in elderly patients (> 70 years) [4].

As our population ages in the era of improved screening, new technology, diagnostic techniques, and novel surgical approaches, candidates for pelvic exenteration are also evolving. Studies examining the effect of age in patients undergoing exenterative surgery remain limited [3, 5–8]. Previous literature mainly describes single institution experiences, reporting on clinical features associated with outcomes but none with age evaluated as a primary risk factor [6, 7, 9]. The purpose of this study is to determine if age at the time of exenteration has an independent impact on surgical complications or overall survival.

Methods

Following approval by The University of Texas MD Anderson Institutional Review Board, a retrospective review of all women who underwent a pelvic exenteration by the Department of Gynecologic Oncology & Reproductive Medicine for any indication from January 1993 to December 2010 was performed. Demographic data, operative reports, pathology reports and clinical outcomes were abstracted from medical records. Demographic data included ethnicity, body mass index, age, and cancer diagnosis. Related co-morbidity information including smoking history, hypertension, diabetes, and pulmonary disease were also collected. Pathologic data including histology, tumor size, lymph node status, and margin status were ascertained. Preoperative laboratory data including hemoglobin, platelet count, creatinine, and albumin were collected to determine if differences existed.

The patients were stratified into three age groups (young: < 50 years, middle: 51–64 years, and senior: ≥ 65 years) based on previously published literature examining surgical outcomes stratified by age [10]. Comparisons between the groups were performed to determine if surgical outcomes, complication rates, and survival were different among the age groups. Post-operative complications were categorized as early (<60 days) or late (≥ 60 days) following exenteration. The sixty days cutoff was chosen based on previously published data and the long convalescence period for these patients [6]. Complications reported included wound separation, infections, urinary (ureteral injury, stricture, renal failure), gastrointestinal (bowel obstruction, colostomy complications), cardiovascular (myocardial infarction, deep vein thrombosis, pulmonary embolism), or need for re-operation. Follow up data including recurrence, time to recurrence, site of recurrence, treatment at time of recurrence and survival status at the time of analysis was also gathered. Time to recurrence was defined as the time interval between exenteration and clinical or radiological diagnosis of disease recurrence. Overall survival was defined as time interval from exenteration to date of death or date of last follow up.

Statistical tests of association were conducted by Fisher's exact test for categorical variables or Kruskal-Wallis test for continuous variables. For the analysis comparing complications by age, two tests were performed: (1) complications <60 days versus no complications and (2) complications ≥ 60 days versus no complications. Kaplan-Meier survival curves were compared using a log-rank test. We generated multivariate logistic regression and Cox proportional hazard models to adjust for confounding variables. We created two equations, one to compare patients 51–65 years old to patients ≤ 50 years old and another to compare >65 years old patients to ≤ 50 years old patients. In building these models we chose all complications that were statistically significantly associated with age ($p < 0.10$) using results from the univariate analysis. The full model was then modified using backward selection, keeping only those terms with $p < 0.05$. Stata (SE 12.1) program was used to perform all statistical analyses.

Results

A total of 161 pelvic exenterations were performed for the following indications: primary (17, 10.6%), recurrent (124, 77.0%), or persistent disease (20, 12.4%) of the cervix, vulva, vagina, or uterus. Among the entire group, total pelvic exenteration was performed most frequently (68.3%), followed by anterior exenteration alone (21.7%), then posterior exenteration alone (9.94%). In this analysis, three patients required a second exenterative procedure and were considered twice. One patient initially had an anterior exenteration for recurrent endometrial adenocarcinoma and underwent a posterior exenteration for recurrent disease three years later. The other two patients initially had posterior exenterations for recurrent vulvar carcinoma and developed disease recurrence requiring anterior exenteration at 10 and 21 months.

There were 58 patients (36.0%) younger than age 50 at the time of exenteration, 62 (39.0%) in the middle aged cohort, and 41 (25.0%) in the senior age cohort. Patient demographics are summarized in Table 1. Body mass index did not differ significantly among the three age groups (28.6, 29.2, and 27.1 kg/m² for young, middle, and senior respectively, $p = 0.5616$). The majority of women were white with senior women being predominantly white compared to middle and young groups ($p = 0.0308$). There were 86 (53.0%) women with cervical cancer, 38 (24.0%) with vaginal cancer, 21 (13.0%) with vulvar cancer, 15 (9.00%) with endometrial cancer, and one (0.010%) with a cancer classified as other (pelvic mucinous tumor of low malignant potential). Recurrent disease was the most common indication for surgery across all three age groups (84.5%, 79%, and 63.4%). Women in the senior cohort were more likely to undergo surgery for primary indications compared to the other age groups ($p = 0.0310$). Cancer diagnosis differed by age group. Women in the young group predominantly had cervical cancer (82.8%) while women in the senior group had mainly vulvar or vaginal cancer (70.7%). Women in the young cohort had a shorter time from diagnosis to exenteration but was not significant compared to women in the middle and senior cohorts (median 14.6 versus 24.8 versus 28.8 months, $p = 0.5600$).

Preoperative factors are listed in Table 2. There was a significant difference among the age cohorts in regard to kidney function as measured by creatinine (0.9 mg/dL, 0.8 mg/dL, 1.0 mg/dL for young, middle and senior, $p = 0.0004$). There was no difference in nutritional status as measured by albumin (mean 4 g/dL, 3.8 g/dL, and 3.8 g/dL, $p = 0.3120$). There were no significant differences in the smoking status among the 3 groups ($p = 0.3110$). Younger women were less likely to have hypertension ($p < 0.0001$) and pulmonary disease ($p = 0.0400$). There were no significant differences among the cohorts in regard to diabetes.

Table 3 summarizes surgical and pathologic characteristics. The most common histologic cell types were squamous cell (60.9%) and adenocarcinoma (22.4%). Thirteen patients

received intraoperative radiation therapy but this did not differ among age groups. There was a significantly longer operating time for women in the younger cohort (10.1 hours) compared to the 9.5 hours in the middle cohort and 8.5 hours in the senior age cohort ($p=0.0089$). Pre-operative hemoglobin was similar across young, middle, and senior cohorts (mean 12.5 G/DL, 12.1 G/DL, 12.2 G/DL respectively; $p=0.8298$) and there was no difference in blood transfusions ($p=0.3478$). There were no significant differences in estimated blood loss or hospital length of stay among the three groups. The majority of women had an incontinent conduit (70.8%) procedure compared to only 29.2% with a continent diversion ($P<0.0001$). Women in the senior cohort were more likely to have an incontinent conduit compared to women in the young cohort ($p=0.0010$). For women undergoing vaginal reconstruction, the majority of women had either a gracilis flap (58, 36.0%) or a VRAM (46, 28.6%) flap. Women in the young and middle cohorts were more likely to have vaginal reconstruction than senior women. Young women tended to have more VRAM procedures than the other age groups ($p=0.0457$). There was no difference in number of intra-operative complications among age groups ($p=0.7130$).

Acute (<60 days following surgery) and late (≥ 60 days following surgery) postoperative complications are detailed in Table 4. The overall incidence of post-operative complications for young, middle, and senior age groups was 89.7%, 87.1%, and 87.8% respectively with no significant differences between groups ($p=0.8863$). The most common acute post-operative complications were related to the urostomy in 39.0% and wound separation occurring in 31.0% of women. Ureteral stricture, ureteral injury, renal failure and venous thromboembolism (VTE) were the most common late complications. On multivariate logistic regression analysis comparing middle aged patients to young patients, length of surgery (OR 0.76, 95% CI 0.60–0.98, $p=0.0320$) was shorter as age increased and bowel obstruction (OR 6.69, 95% CI 1.15–39.03, $p=0.0350$) was the only factor that occurred more frequently in the middle aged patients. Similarly, on multivariate logistic regression analysis comparing senior patients to young patients, length of surgery (OR 0.67, 95% CI 0.46–0.96, $P=0.0300$) was the only factor that was shorter as age increased.

Clinical outcomes are summarized in Table 5. The median time to follow up was 21 months for the young age group, 33 months for the middle age group, and 19 months for the senior age group. Following exenteration, there were 83 recurrences (53.5%) and the majority occurred at distant sites (not in the pelvis) (63.1%). The overall recurrence rates following exenteration in the young, middle, and senior age groups were 68.4%, 46.7%, and 42% respectively ($p=0.0165$). The site of recurrence was not significantly different across the three groups ($p=0.0830$). Although recurrence rates were highest in the young cohort, time to recurrence was less from exenteration to recurrence in the middle and senior cohorts compared to the young cohort (HR=0.54, $p=0.021$; HR= 0.41, $p=0.0170$ respectively). Time to death among groups, however, was not significantly different. Treatment at the time of recurrence following exenteration varied widely with the majority receiving either no further treatment (47.6%) or chemotherapy alone (47.6%). Overall, there was no significant difference in treatment for recurrence after exenteration based on age ($p=0.4071$). Kaplan-Meier survival estimates for time to recurrence and overall survival are depicted in Figure 1.

Discussion

Our study did not demonstrate major differences in complications or survival for women 65 years old compared to younger women at the time of pelvic exenteration. While senior women were more likely to have co-morbid conditions (hypertension and pulmonary disease) this did not translate to increased morbidity or shorter survival. Neither early nor late post-operative complications were significantly different among the cohorts.

While factors such as tumor size, pelvic sidewall involvement, lymph node status, margin status, and time from primary diagnosis are generally believed to affect survival, other factors such as age and BMI are more controversial [3, 5–7, 18]. In 1992, Matthews et al performed a retrospective review of 63 patients age 65 years or older that underwent a pelvic exenteration at our institution. The mean age at surgery was 70 years with a range from 65 to 80 years with a median follow up of 48 months. Morbidity and mortality rates were comparable to those previously reported in the literature for younger patients with similar 5-year survival rates. Thus, the authors concluded that advanced age alone should not be a contraindication to exenteration [3]. Data from our current study strengthens the support for offering women over 65 years of age a pelvic exenteration by directly comparing them to younger women who underwent the same procedure during the same time period.

We attempted to identify pre-operative factors that may have contributed to an increase in morbidity and mortality for pelvic exenteration. We found that women in the young cohort had less co-morbid conditions compared to the senior women. Not surprisingly, young women had significantly better renal function as measured by creatinine levels, consistent with an expected change in kidney function in the aging process. In addition, elderly women were more likely to have hypertension and pulmonary disease. While the pre-operative co-morbidities were higher in the senior women, this did not result in an increase in morbidity and mortality.

We found no difference in length of hospital stay and estimated blood loss. Previously published literature has reported a median operative time of 5.42 to 7.75 hours, a median length of hospital stay of 10–29 days, and an estimated blood loss of 1–3.1 liters [5, 6, 8, 9]. Our data is consistent with published literature. There were no differences between groups with regards to lymph node status or adequate surgical margins. The shorter operative time in the elderly cohort was likely in part due to the decreased number of vaginal reconstructions and continent urinary reservoirs performed in the elderly cohort compared to the younger groups.

Postoperative complications were similar between the three cohorts. While our complication rates appear to be at the higher than those previously reported (38–86%), this is possibly a consequence of reporting variation [3, 6–8, 18]. In our study, we report the total number of patients that had at least one postoperative complication including either early or late complications. We noted greater complication rate in the early postoperative period compared to late complication, primarily due to the high incidence of superficial wound separation. However, there was no difference in overall complications stratified by age.

In our patients recurrence rate was higher in the young cohort while the median time to recurrence was longest in the middle age group with no difference in median follow up. Several factors may contribute to higher recurrence rate in young patients such as tumor biology and selection bias. Factors such as tumor size, grade, pelvic sidewall involvement, and lymph node involvement portends a worse prognosis however in our younger cohort, there may have been a higher likelihood of being dispositioned to surgery. There was no difference among the groups in overall survival.

The strengths of this paper are the large sample size as well as the stratification of patients into cohorts based on age that allowed for direct comparisons. We limited the risk of confounding factors by performing a multivariate logistic regression analysis. While this study was performed at a single institution, several different surgeons participated accounting for some practice variation. In addition, some procedures were done by multi-specialty surgeons (including plastic surgery for reconstruction) while others were performed solely by gynecologic oncologists. This study is limited by its retrospective

nature as well as selection bias, particularly in the elderly cohort, as we report only the patients who were offered an extenteration and were likely the best surgical candidates selected. In addition, while the overall sample size is large for this patient cohort, the subgroups may not be large enough to detect significant differences in rare outcomes.

In conclusion, advanced chronological age should not be considered a contraindication to a potentially curative surgical procedure. When patients are stratified by age, the duration of surgery, blood loss, length of hospital stay, and complication rates do not increase with increasing age. A variety of patient characteristics and peri-operative factors interplay in determining the most appropriate candidate for a pelvic exenteration procedure. This study indicates that pelvic exenteration can be offered to select patients without considerable increase in morbidity due to age alone.

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Highlights

- There was no difference in surgical complication rates or survival after pelvic exenteration based on age at the time of surgery.
- Advanced age alone should not be a contraindication to pelvic exenteration.

Figure 1.
Kaplan-Meier curves for (A) time-to-recurrence and (B) time-to-death

Table 1

Demographics Factors by Age Group

	Young (n = 58)	Middle (n = 62)	Senior (n = 41)	p-value
Mean Age at Diagnosis (years)	40	57	71.7	
Range	(24.8–49.9)	(50.1–64.7)	(65.5–85.9)	
Mean Age at Exent (years)	37.9	56.6	70.5	
Range	(21.3–49.6)	(50.5–63.7)	(65.5–78.7)	
Mean BMI	28.6(15.2–50.3)	29.1 (15–50.8)	27.1 (15.2–37.9)	0.5616
Race				
White	39 (67.2%)	39 (62.9%)	36 (87.8%)	0.0308
Black	4 (6.9%)	6 (9.7%)	0	
Asian	2(3.4%)	0	1 (2.4%)	
Hispanic	7(11.9%)	14(31.8%)	15 (25.9%)	
Other	13 (22.4%)	17 (27.4%)	4 (9.8%)	
Cancer Diagnosis				
Cervix (n=86)	48 (82.8%)	29 (46.8%)	9 (22%)	<0.0001
Vulva (n=21)	6 (10.3%)	4 (6.5%)	11 (26.8%)	
Vagina (n=3 8)	3 (5.2%)	17 (27.4%)	18(43.9%)	
Uterus (n= 15)	1 (1.7%)	11(17.7%)	3 (7.3%)	
Other (n=1)	0	1 (1.6%)	0	

Table 2

Factors Affecting Surgery Performance Stratified by Age

	Young (n = 58)	Middle (n = 62)	Senior (n = 41)	p-value
BUN	10	12.3	14.4	<0.0001
Range	(1.6–2.0)	(5–21)	(3–27)	
Creatinine	0.8	0.8	0.9	0.0004
Range	(0.4–9)	(0.5–1.6)	(0.5–1.8)	
Pre-albumin	4	3.8	3.8	0.312
Range	(1.8–5.3)	(2–4.8)	(1.8–4.8)	
Smoking				0.311
Never (n=97)	34 (58.6%)	39 (65.9%)	24 (58.5%)	
Current (n=30)	15 (25.9%)	10(16.1%)	5 (12.2%)	
History (n=34)	9(15.5%)	13 (21%)	12 (29.3%)	
Co-morbidities				<0.0001
HTN	4 (6.9%)	16 (25.8%)	20 (48.8%)	
DM	2(3.4%)	10(16.1%)	5 (12.2%)	
Cardiac disease	1 (1.7%)	1 (1.6%)	12 (29.3%)	
Pulmonary disease	0	3 (4.8%)	4 (10%)	

Table 3

Univariate analysis of surgical and pathologic factors: young patients had significantly longer surgery time.

	Young (n = 59)	Middle (n = 62)	Senior (n = 41)	p-value
Type of Exenteration				0.847
Total (n=103)	37(63.8%)	41 (66.1%)	25 (61%)	
Anterior only (n=35)	13 (22.4%)	14 (22.6%)	8 (19.5%)	
Posterior only (n=23)	8(13.8%)	7(11.3%)	8 (19.5%)	
Surgical Measures				
EBL (mL)	2100 (280–9300)	2000 (700–16500)	1950 (700–13000)	0.992
Surgery Length (hrs)	10.1 (6.1–15.4)	9.5 (4.6–15.5)	8.5 (4–15.1)	0.009
Vaginal Reconstruction				0.046
None	4 (6.9%)	14 (22.6%)	12 (29.3%)	
Gracilis flap	22 (37.9%)	25 (40.3%)	11 (26.8%)	
VRAM	21 (36.2%)	14 (22.6%)	11 (26.8%)	
Omental/skin graft	3 (5.2%)	1 (1.6%)	0	
Primary closure	6(10.3%)	8 (12.9%)	7 (17.1%)	
Other	2 (3.4%)	0	0	
Urinary procedures				
Continent (n=42)	24 (45.3%)	17 (29.8%)	1 (2.9%)	<0.0001
Incontinent (n=102)	29 (54.7%)	40 (70.2%)e	33(97.1%)	
Intraoperative radiation	5 (8.6%)	6 (9.7%)	2 (5.0%)	0.7130
Lymph Node Status				0.863
Negative (n= 13 4)	49 (84.5%)	52(83.9%)	33 (80.5%)	
Positive (n=12)	5 (18.6%)	5(8.1%)	2 (4.9%)	
Missing	4 (6.9%)	5(8.1%)	6 (14.6%)	
Length of Stay (days)	19.6 (7–48)	19.2 (8–97)	18.7(5–63)	0.237
Histology				0.043
Squamous	36(62.1%)	35 (56.4%)	27 (65.9%)	
Adenocarcinoma	17 (29.3%)	15 (24.2%)	4 (9.8%)	
Adenosquamous	3 (5.2%)	2 (4.8%)	0	
Melanoma	1 (1.7%)	2 (3.2%)	5 (12.2%)	
Clear cell	0	1 (1.6%)	0	
Other	1 (1.7%)	6 (9.7%)	3 (7.3%)	
Unknown	0	0	2 (4.9%)	
LVS1				0.746
Yes	36(62.1%)	42 (67.7%)	25 (61%)	
No	22 (37.9%)	20 (32.3%)	16 (39%)	

	Young (n = 59)	Middle (n = 62)	Senior (n = 41)	<i>p</i> -value
Margin Status				0.7787
Negative	49 (84.5%)	54 (85.5%)	33 (80.5%)	
Positive	9(15.5%)	8 (12.9%)	8 (19.5%)	
Unknown	0	1 (1.6%)	0	

Table 4

Univariate analysis of early (<60 days) and late (>60 days) post-operative complications

	Early postoperative complications <60 days				Late postoperative complications >60 days			
	Young (n=58)	Middle (n=62)	Senior (n=41)	p-value	Young (n=58)	Middle (n=62)	Senior (n=41)	p-value
Wound separation	16 (27.6%)	17 (27.4%)	14 (34.1%)	0.7977	1 (1.7%)	2 (1.2%)	0	0.7878
Infection								
Abscess	8 (13.6%)	13 (21%)	5 (12.2%)	0.4626	5 (8.6%)	2 (3.2%)	1 (2.4%)	0.5629
Sepsis	3 (5.2%)	7 (11.3%)	4 (9.8%)	0.5274	2 (3.4%)	0	0	0.3388
Pneumonia	3 (5.2%)	8 (12.9%)	4 (9.8%)	0.355	1 (1.7%)	0	1 (2.4%)	0.7194
Urinary								
Ureteral Stricture	2 (3.4%)	3 (4.8%)	0	0.4433	2 (3.4%)	6 (9.7%)	3 (7.3%)	0.4212
Ureteral Injury	4 (6.9%)	4 (6.5%)	1 (2.4%)	0.6273	6 (10.3%)	8 (12.9%)	1 (2.4%)	0.1661
Renal Failure	2 (3.4%)	4 (6.5%)	0	0.24	4 (6.9%)	3 (4.8%)	1 (2.4%)	0.5329
Urostomy Complications	17 (29.3%)	17 (27.4%)	8 (19.5%)	0.6221	9 (15.5%)	7 (11.3%)	5 (12.2%)	0.7175
Kidney Stones	N/A	N/A	N/A	9 (15.5%)	4 (6.5%)	2 (4.9%)	0.1661	
Gastrointestinal								
Bowel Obstruction	6 (10.3%)	6 (9.7%)	4 (9.8%)	>0.9999	5 (8.6%)	9 (14.5%)	0	0.2563
Complications	4 (6.9%)	3 (4.8%)	4 (9.8%)	0.5221	2 (15.5%)	1 (1.6%)	0	0.6186
Cardiovascular								
DVT	0	2 (3.2%)	1 (2.4%)	0.4882	6 (10.3%)	2 (3.2%)	0	0.0748
MI	0	1 (1.6%)	0	0	0	1 (2.4%)	0.2563	
Reoperation	5 (8.6%)	7 (11.3%)	3 (7.3%)	0.8336	0	2 (3.2%)	1 (2.4%)	0.4779

Table 5

Clinical outcomes

	Young (n=58)	Middle (n=62)	Senior (n=41)	p-value
Median follow up (mo)	21.13	33.23	19.38	0.4451
Recurrence rate	39 (68.42%)	28 (46.67%)	16(42.11%)	0.0164
Median time to recurrence (mo)	30.09	52.37	33.52	0.0109
Site of recurrence				0.0829
Pelvis (n=28)	11(27.5%)	8 (28.6%)	9 (56.3%)	
Distant (n=53)	27 (67.5%)	20(71.4%)	6 (37.5%)	
Unknown (n=3)	2 (5.0%)	0	1 (6.3%)	
Treatment at recurrence				0.4071
None	6(1.5%)	8 (28.6%)	6 (37.5%)	
Radiation alone	3 (7.5%)	1 (3.6%)	2 (12.5%)	
Chemotherapy alone	11 (27.5%)	6(21.4%)	3 (18.8%)	
Surgery	3 (7.5%)	2(7.1%)	3 (18.8%)	
Chemoradiation	6(15%)	6(21.4%)	0	
Surgery+ chemotherapy	4 (10%)	1 (3.6%)	1 (6.3%)	
Surgery + radiation	2 (5%)	0	1 (6.3%)	
Surgery + chemoradiaton	1 (2.5%)	3 (10.7%)	0	
Chemotherapy +hormone	1 (2.5%)	0	0	
Unknown	3 (7.5%)	1 (3.6%)	0	
Current status				0.1305
NED	17 (29.3%)	23(37.1%)	11 (26.8%)	
Alive with disease	2 (5.2%)	2(3.2%)	1 (2.4%)	
Died of disease	31 (53.4%)	21 (33.9%)	15 (36.6%)	
Died of complication	1 (1.7%)	3 (4.8%)	2 (4.9%)	
Died of other	3 (5.2%)	7(11.3%)	2 (4.9%)	
Died of unknown reason	3(5.2%)	6 (9.7%)	10 (24.4%)	