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Survival outcomes improved in contemporary cohort of patients with pelvic or abdominal recurrence after treatment for Stage I/II endometrial carcinoma

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Abstract

Objectives—Pelvic and abdominal recurrences in Stage I/II endometrial carcinoma are associated with poor outcomes, yet prognostic factors for survival after recurrence are not well-described. Herein we identify patients with pelvic or abdominal recurrence after surgery for Stage I/II endometrial carcinoma and describe symptoms at presentation, prognostic factors, and salvage treatment toxicity.

Methods—This is a retrospective cohort of 20 consecutively treated patients with recurrence after treatment for Stage I/II endometrial carcinoma followed by our Institution's Radiation Oncology Department from 1998-2015.

Results—The median time to pelvic or abdominal recurrence was 18.1 months (range, 4.2-59.6 months), with 50% of recurrences at extra-nodal locations. Two year progression-free survival (PFS) was 44% and 2 year overall survival (OS) was 82%. Salvage treatments varied widely, including chemotherapy and radiation therapy (RT) (7), surgery and RT (3), and surgery, chemotherapy, and RT (3). On univariate analysis of PFS, symptoms at recurrence ($p=0.04$) and extra-nodal recurrences ($p<0.01$) were found to be statistically significant negative prognosticators for PFS. On univariate analysis of OS, increasing age at recurrence and presence of symptoms were found to have a trend toward statistically significant association with negative OS outcomes ($p=0.08$ and $p=0.10$, respectively).

Conclusions—Our study demonstrates long-term survival for pelvic or abdominal recurrences is possible with curative salvage therapy. The presence of symptoms is a negative prognostic factor in treatment outcome and imaging may be effective for diagnosis in symptomatic and asymptomatic patients. Larger studies need to be performed to confirm these findings.

Keywords

Stage I/II endometrial carcinoma; pelvic recurrence; abdominal recurrence; prognosis; symptoms

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Introduction

Endometrial carcinoma is the most frequently diagnosed gynecological cancer in America, with an incidence of nearly 45,000 annually.¹ Though clinical practice differs regarding whether, when, and how to deliver radiotherapy (RT) for patients with Stage I/II endometrial cancer, RT has been shown to significantly improve local control of disease.²⁻⁸ Among patients treated by surgery alone, up to 15% experience locoregional relapse, with pelvic recurrences accounting for 10-50% of these relapses.^{5,9,10} Historically, pelvic recurrence carries a poor prognosis. Compared to salvage outcomes for vaginal recurrence alone where 5-year survival is estimated to be 40-75%, outcomes for pelvic recurrence are significantly poorer, with survival as low as 8% at 3 years.¹⁰⁻¹³

Despite the well-documented poor outcomes for patients with pelvic recurrence after hysterectomy, literature on symptoms at presentation, prognostic indicators, and toxicity of treatment are limited. Symptoms reported for pelvic recurrence tend to be grouped into those reported for locoregional recurrence and are therefore undifferentiated from symptoms of vaginal recurrence.¹⁴ Prognostic factors for outcomes after salvage RT for isolated vaginal relapses of endometrial cancer have been well described, though how these factors impact the subset of patients with pelvic recurrence remains unclear.^{9,14,15} Herein we seek to characterize the symptoms, salvage outcomes, toxicities, and prognostic indicators for progression-free survival (PFS) and overall survival (OS) in patients with pelvic or abdominal recurrences after definitive treatment for Stage I/II endometrial carcinoma.

Materials and Methods

Patient selection

This retrospective study was approved by our Institution's IRB. The records of all 657 patients with Stage I/II endometrial carcinoma from 1998 to 2015 at our Institution were reviewed. Twenty consecutively treated patients were found to have pelvic or abdominal recurrence requiring salvage therapy, 13 of whom had pathologic diagnoses of recurrent disease, six with empiric diagnoses based on serial imaging or PET/CT studies, and one with indeterminate diagnostic methodology (referred patient without documentation of recurrence diagnosis methodology). Patients with isolated vaginal relapses without disease elsewhere were excluded from analysis. Chart reviews were conducted to identify symptoms at presentation, salvage outcomes, toxicity, and prognostic factors for PFS and OS.

Definition of variables

Initial tumor size was defined by largest dimension in centimeters. Initial tumor grade was defined as grade 1, 2, or 3 by pathology of the surgical specimen. Initial tumor histology was defined as endometrioid adenocarcinoma or high-risk histology (papillary serous, clear cell, mixed endometrial with papillary serous or clear cell, or carcinosarcoma). Recurrence location was defined as isolated to lymph nodes only (with or without vaginal recurrence) or involvement of pelvic, peritoneal, or retroperitoneal organs (with or without lymph node involvement). Radiotherapy toxicity outcomes were graded according to the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment

of cancer (EORTC) consensus criteria.¹⁶ Chemotherapy toxicity outcomes were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Time to recurrence was defined from date of initial diagnosis to date of recurrence diagnosis. Time to progression was defined from date of recurrence diagnosis to date of re-recurrence diagnosis. Follow-up time defined from date of recurrence diagnosis to date of most recent visit to a medical, radiation, or gynecologic oncologist. Overall survival endpoint was all-cause mortality, and disease-specific survival endpoint was death caused by progressive endometrial carcinoma.

Statistical analysis

Statistical analysis was done using the STATA program (StataCorp, College Station, TX). In selection of candidate prognostic factors for PFS and OS, we included those previously found to be prognostic factors in recurrent early-stage endometrial carcinoma: age, size of recurrence, time interval from hysterectomy, initial grade, initial histology, and location of recurrence.^{9,15} In addition, we included receipt of adjuvant RT or chemotherapy, symptoms at recurrence, and RT, surgery and chemotherapy as salvage treatment. Log-rank tests, Cox proportional-hazard analysis, and Kaplan-Meier method was used for time-to-event analysis.

Results

Patient Characteristics and Outcomes

Individual patient clinical histories are detailed in Table 1 with a total of 20 patients meeting criteria for analysis. The median age at initial diagnosis was 62 years (range, 33-91 years). Sixteen patients had full surgical staging, including total hysterectomy and pelvic and para-aortic lymphadenectomy, at time of hysterectomy; ten patients were found to have FIGO Stage IA disease and seven had FIGO Stage IB disease. One-third of patients were classified as having higher risk histologies of clear cell, serous, papillary serous carcinoma, or carcinosarcoma. Approximately 60% of the patients received adjuvant RT. Three received external beam RT (EBRT) with median dose of 5040 cGy (range, 4500-5040 cGy) and nine received high-dose rate (HDR) vaginal brachytherapy with median dose of 2100 cGy (range, 1500-2500 cGy). Only two patients received adjuvant carboplatin-paclitaxel combination chemotherapy.

The median time to pelvic or abdominal recurrence after initial treatment was 18.1 months (range, 4.2-59.6 months). Median follow-up time after diagnosis of recurrence was 35 months (range, 8-156 months). Recurrences were isolated to pelvic or para-aortic lymph nodes with or without vaginal cuff recurrence in 50% of cases. The other 50% of recurrences involved extra-nodal locations such as the rectum and psoas muscles (Table 1). The median recurrence tumor size was 3.3 cm (range, 1.6-16.0 cm). Salvage treatment regimens varied widely, with seven cases of chemotherapy and RT, three cases of surgery and RT with or without sensitizing cisplatin, three cases of trimodality therapy (surgery, chemotherapy, and RT), one case of surgery and chemotherapy, and six cases of single modality therapy. For non-nodal disease and limited nodal disease (either by size or number), surgical resection was attempted if feasible and followed by adjuvant RT. If surgical resection was not performed, then treatment to the involved nodal region (i.e. pelvis or para-aortic) was

performed with boost doses of up to 6000 cGy to gross disease. Fifteen patients received salvage EBRT with median dose of 5040 cGy (range, 3500-5040 cGy), five patients received EBRT boost of 1200 or 2700 cGy and two patients received HDR vaginal brachytherapy of 900 or 1600 cGy. Carboplatin-paclitaxel combination delivered before and after RT was the most common chemotherapy given to 89% of patients.

In 67% of cases, recurrence was diagnosed as a result of patient symptoms. The most common symptoms were pain (abdominal pain in four patients, pelvic pain in three, and back pain in one) and bleeding (rectal bleeding in three patients and vaginal bleeding in one) (Table 2). Two patients were diagnosed after symptom development despite recent imaging within six months of diagnosis. Of the four asymptomatic patients diagnosed on routine imaging, three were identified by routine imaging for endometrial cancer surveillance, which found enlarged lymph nodes in those followed with six month scans and an aorto-caval mass in one patient followed with a 12 month scan. One asymptomatic patient was diagnosed by CT imaging to evaluate an unrelated submucosal colonic nodule. Only one recurrence was directly diagnosed as a result of elevated Ca-125 levels, though 54% of patients were found to have elevated Ca-125 levels at the time of recurrence diagnosis. All patients had measurable disease on either CT or MR imaging, regardless of symptoms at presentation or recurrence location.

Of the 20 patients treated for recurrence, nine patients remain progression-free, five patients developed locoregional re-recurrence representing in-field failure, three developed distant disease, and one had progressive disease despite treatment. Median time to local progression was 8 months and median time to distant disease was 9 months.

Currently, 50% are without evidence of disease (no evidence of disease, NED), 17% are alive with disease (AWD), and 33% died of disease (DOD). The median PFS time was 12 months (range, 4-90 months) with 2 year PFS of 44%. The 2 year OS was 82% and 4 year OS was 57%. Of note, all deaths were caused by progressive endometrial cancer. Therefore, disease-specific survival was identical to OS.

Prognostic factors

On univariate analysis of PFS, symptoms at recurrence ($p=0.04$) and recurrence location ($p<0.01$) were found to be statistically significant prognostic variables, with the presence of symptoms and non-lymph node recurrences as negative prognosticators for PFS (Table 3). Patients with nodal recurrences had 2 year PFS of 86% whereas extranodal recurrences had 2 year PFS of 11%. Those who did not have symptoms had 2 year PFS of 100% whereas those with symptoms had 2 year PFS of 30%. Kaplan-Meier curves were generated to illustrate the effect of symptoms and recurrence location on PFS (Figure 1A). We evaluated whether these variables were related since symptoms such as pain and bleeding frequently arise as a result of increased tumor mass and tumor involvement of key organs. Indeed, the presence of symptoms was closely associated with recurrence location ($p < 0.01$).

On univariate analysis of OS, increased age at recurrence ($p = 0.08$) and presence of symptoms at recurrence ($p = 0.10$) were variables that demonstrated a trend toward statistical significant association with negative OS outcomes. Those who did not have

symptoms at recurrence had 2 year OS of 100%, whereas those who were symptomatic at presentation had 2 year OS of 67%. Kaplan-Meier curves were generated to illustrate the effect of symptoms and age at recurrence on OS (Figure 1B). Of note, recurrence location, which was found to be a significant prognostic variable for PFS, was not found to be a significant prognostic variable for OS.

On multivariate models of PFS and OS incorporating all univariate variables with $p < 0.10$, there was no demonstration of statistically significant associations of any variable with PFS or OS.

Toxicity

Fifty-six percent of patients did not experience late toxicities from salvage treatment. Of the eight that experienced late toxicities, two developed grade 1 toxicities (urinary urgency and vaginal telangiectasias) and three had grade 2 toxicities (lymphedema requiring compression stockings, chronic diarrhea, and symptomatic sensory neuropathy). Three patients developed grade 4 toxicities; one patient developed recurrent small bowel obstructions requiring total parenteral nutrition and two developed rectovaginal fistulas. All three of these patients with grade 4 toxicities presented with extranodal recurrent disease. The rectovaginal fistulas developed in patients who did not have a history of adjuvant RT. Of the patients who developed late toxicities from salvage treatment and who had a history of adjuvant chemotherapy or RT, one developed grade 4 recurrent small bowel obstructions, one developed grade 1 vaginal telangiectasias, and one developed peripheral neuropathy. No late hematologic toxicities were documented.

Discussion

Our study presents results of multimodality therapy for patients with recurrent pelvic or abdominal disease from endometrial cancer. Our results demonstrate that long-term survival is possible with curative salvage therapy after pelvic or abdominal recurrences of endometrial carcinoma.

Two year PFS and OS was 44% and 82%, respectively. This compares favorably to prior studies reporting rates of long-term survival of 29% and 18% at 5 and 10 years, respectively, for pelvic recurrences.^{6,17,18} Prior studies, however, were retrospective reviews of patients treated from 1977-1987⁶ and 1980-1995¹⁸. Changes in the endometrial carcinoma treatment paradigm since these decades may account for some of these differences. Advancement in high resolution imaging contributes to more sensitive localization of locoregional and distant recurrences. The increased utilization of IMRT and proton therapy may contribute to more precise dose delivery. Chemotherapy regimens have also changed. In the analysis by Sartori *et al.*, the common chemotherapy choices were adriamycin, cisplatin, and cyclophosphamide in different combinations.¹⁸ In this study, the most common chemotherapeutic regimen was carboplatin-paclitaxel given before and after RT, which has demonstrated superior survival outcomes and toxicity profiles in adjuvant treatment of advanced endometrial carcinoma in the past decade.¹⁹⁻²¹

This prognostic PFS and OS variables identified in this pelvic recurrence study differ from historical studies that include pelvic, vaginal, and distant recurrences. In previous studies, age at recurrence (<65 years), advanced stage at original surgery, extravaginal recurrence location, presence of adjuvant RT, and longer progression-free interval prior to recurrence were statistically significant prognostic variables associated with improved OS.^{6,18} In this study, all these variables were assessed, but only age at recurrence (<65 years) and the absence of symptoms were nearly significant prognostic variables for improved overall survival ($p=0.08$, 0.10 , respectively). PFS prognostic variables have not been reported in these previous studies, but we found that the presence of symptoms ($p=0.04$) and extranodal location of recurrence (<0.01) were significantly associated with poor PFS on univariate analysis. The traditional prognostic variables for PFS and OS in recurrent endometrial cancer may therefore be different in the pelvic recurrence subgroup. While this study is limited by smaller sample size, it is also one of the few studies reported in the literature looking exclusively at pelvic recurrences with or without vaginal cuff involvement. The prognostic variables identified herein require further evaluation before application in clinical decision-making for patients with pelvic recurrences of early stage endometrial cancer.

Amongst patients with symptoms at presentation, 2 year PFS and OS was 30% and 67%, respectively, compared to 100% and 100%, respectively, in asymptomatic patients. Consistent with prior studies, approximately half of patients with recurrence experienced symptoms, the most frequent of which was pain (abdominal, back, pelvic, and bony pain).⁶ In this study, the presence of symptoms was associated with poor PFS ($p=0.04$) and had a trend toward association with poor OS ($p=0.10$). The separation of survival curves seen in Figure 1, especially when detectable in a small cohort of patients, support results reported in retrospective studies from Italy and the United Kingdom that also found symptoms were negative prognosticators for salvage of pelvic or abdominal recurrence in early stage endometrial cancer.^{22,23} In the current study, salvage success rates (100% at 2 years) in asymptomatic patients were substantially higher than historical salvage success rates for all patients with pelvic recurrence, which range from 15% to 30%.¹⁷ Importantly, all six asymptomatic recurrences in this study were diagnosed by routine abdominal or pelvic imaging at 6-12 month intervals and all symptomatic recurrences were visible on CT or MR imaging. Therefore, the survival advantage with asymptomatic recurrences and feasibility of CT or MR to identify recurrences indicate imaging remains a powerful tool to identify pelvic or abdominal recurrences before symptoms develop.

Salvage treatment was generally well-tolerated, even in individuals who previously received adjuvant chemotherapy or RT. No hematologic toxicities were documented, consistent with previous reports of the superior toxicity profile of sandwiched carboplatin-paclitaxel with RT.^{21,24} Only one patient developed symptomatic peripheral neuropathy. Of the three patients who developed grade 4 toxicity, only one had a history of prior adjuvant vaginal brachytherapy. Therefore, in this cohort, we found that salvage treatment was safely administered in patients regardless of prior exposure to surgery, chemotherapy, and/or RT. However, because grade 4 toxicity was found in 15% of cases, patients should continue to be counseled regarding the potential for significant treatment toxicity.

Our study has important limitations, including the small number of patients in our analysis. As with any retrospective study, it is prone to selection biases particularly with regard to which patients were selected for routine follow up imaging. In our current clinical practice, we obtain lab work or imaging studies every six months in patients who have a combination of high risk features including high grade, lymphovascular invasion, deep myometrial invasion or high risk histology. Given both the extended time period of inclusion of this analysis as well as the lack of well-defined treatments for women with pelvic or abdominal recurrences of endometrial cancer, patients in this analysis received heterogeneous treatment which may also limit the interpretability of our findings.

The issue of pelvic and abdominal recurrence detection is a timely one, as its incidence may be expected to increase in the setting of more prevalent usage of adjuvant vaginal brachytherapy instead of pelvic radiation. This change in practice pattern is motivated by results of PORTEC-2, which concluded vaginal brachytherapy alone for treatment for intermediate risk endometrial carcinoma was comparable to pelvic radiation for local vaginal control.²⁵ However, vaginal brachytherapy alone is anticipated to result in an increased number of isolated pelvic recurrences compared to EBRT (the PORTEC-2 study reports a hazard ratio of 3.1).²⁵ Increased pelvic relapse with vaginal brachytherapy is further noted in the early report of GOG 0249, where patients with high intermediate risk surgically staged endometrial cancer randomized to receive vaginal brachytherapy and chemotherapy had a higher incidence of pelvic relapse compared to patients that received pelvic RT.²⁶ These changes in practice will likely contribute to increased incidence of pelvic and abdominal recurrences that are difficult to detect early without the benefit of anatomic imaging and potentially carry a worse prognosis once symptoms develop. While routine imaging is not recommended, we acknowledge through our experience with this retrospective cohort that it is feasible and effective in detecting pelvic recurrences, especially in asymptomatic patients. In the meantime, we are encouraged by the improved survival outcomes reported in this study compared to those reported 10-20 years ago.

In conclusion, Stage I/II endometrial carcinoma is a common diagnosis with favorable treatment outcomes. Yet, local and regional recurrences do occur, with pelvic recurrences historically associated with especially poor prognoses. Our results demonstrate long-term survival for pelvic or abdominal recurrences is possible with curative salvage therapy, achieving two year PFS and OS of 44% and 82%, respectively. These survival outcomes are improved relative to historical studies. In addition, we identify that the presence of symptoms such as pain and bleeding may be negative prognostic factors in treatment outcome for pelvic recurrences. Our results are hypothesis generating and should be confirmed with larger studies, more standardized treatment protocols, and longer follow-up, especially as the incidence of pelvic recurrence is expected to increase with practice trends shifting to the use of vaginal brachytherapy in place of pelvic radiation.

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Figure 1. Kaplan-Meier curve for PFS and OS. (A) PFS stratified by symptoms (left) and location of recurrence (right). (B) OS stratified by symptoms (left) and age at recurrence diagnosis (right). Hash marks represent censored patients. P-values determined by log-rank tests.

Table 1

Summary of cohort clinical characteristics, treatments, and outcomes. FIGO = International Federation of Gynecology and Obstetrics, EBRT = external beam radiation therapy, Rx = treatment, CA = carcinoma, brachy = HDR brachytherapy, Carbo/Taxol = carboplatin and paclitaxel, LN = lymph node, NED = no evidence of disease, DOD = died of disease, AWD = alive with disease, N/A = not applicable, N = no, TBD = to be determined at next imaging or follow-up, period = unknown.

Age at diagnosis	Initial FIGO Stage	Initial Histology	Initial Grade	Adjuvant RT	Adjuvant Chemo	# Months before recurrence	Recurrence site	Recurrence symptoms	Size of recurrence (cm)	Type of salvage Rx	Disease status at last follow-up
60	IB	Endometroid adenoCA	2	N	N	16.8	Para-aortic LN	Abdominal pain	2.4	EBRT	NED
61	IA	Endometroid adenoCA	2	N	N	14.4	Psoas muscle	Hip and leg pain	10.0	Surgery, Chemo	DOD
57	N/A	Endometrial hypertrophy	N/A	N	N	11.2	Inguinal LN	None	4.8	Surgery, Chemo, EBRT	NED
72	IA	Papillary serous CA	3	N	N	14.3	Pelvic LN and vagina	Vaginal bleeding	4.0	Chemo, EBRT, vaginal brachy	DOD
63	IB	Endometroid adenoCA	2	Vaginal brachy	N	30.1	Psoas, paraspinal mass	Back pain	5.4	Chemo, EBRT	DOD
67	IA	Papillary serous CA	3	N	Carbo/Taxol	23.4	Regional LN	Abdominal pain	3.3	Chemo, EBRT	NED
71	IA	Endometroid adenoCA	3	N	N	36.0	Rectum	Rectal bleeding	.	EBRT	DOD
70	IA	Papillary serous CA	2	Vaginal brachy	Carbo/Taxol	19.4	Rectum	Rectal bleeding	4.3	Surgery, EBRT with sensitizing chemo	NED
56	IB	Papillary serous CA	2	N	N	24.0	Pelvic sidewall, pelvic bone, and pelvic LNs	.	8.7	Chemo, EBRT	DOD
33	IA	Endometroid adenoCA	1	N	N	57.4	Ovaries and pelvic LNs	.	16	Surgery, EBRT	NED
64	IA	Endometroid adenoCA	3	Vaginal brachy	N	21.4	Iliac LNs	None	1.6	Chemo	NED

Age at diagnosis	Initial FIGO Stage	Initial Histology	Initial Grade	Adjuvant RT	Adjuvant Chemo	# Months before recurrence	Recurrence site	Recurrence symptoms	Size of recurrence (cm)	Type of salvage Rx	Disease status at last follow-up
62	IB	Mixed endometroid/cl ear cell	3	Vaginal brachy + EBRT	N	14.1	Adrenal gland	Pelvic pain	6.0	Surgery	NED
60	IB	Endometroid adenoCA	2	Vaginal brachy	N	59.6	External iliac LN	Abdominal pain	2.0	Chemo, EBRT	NED
58	IA	Endometroid adenoCA	2	Vaginal brachy	N	49.7	External iliac LN	None	2.7	Surgery, Chemo, EBRT	NED
61	IB	Endometroid adenoCA	3	EBRT	N	13.7	Para-aortic LN	None	2.0	Surgery, EBRT with sensitizing chemo	NED
71	IA	Endometroid adenoCA	2	Vaginal brachy	N	23.0	Rectosigmoid colon	Rectal bleeding	4.1	Surgery	DOD
62	II	Endometroid adenoCA	2	Vaginal brachy + EBRT	N	12.9	Umbilicus and surgical scars	Abdominal pain	3.0	Surgery, Chemo, EBRT	AWD
68	IA	Endometroid adenoCA	2	N	N	4.2	External iliac LN, obturator	Pelvic pain	2.8	Chemo, EBRT	NED
62	IB	Endometroid adenoCA	1	N	N	6.3	Perirectal LN and vagina	None	1.6	Chemo, EBRT, vaginal brachy boost	TBD
91	II	Carcino-sarcoma	.	Vaginal brachy	N	13.7	Iliac bifurcation LN	None	1.8	EBRT	TBD

Table 2

Frequency of symptoms leading to diagnosis of pelvic or abdominal recurrence in patients previously treated for Stage I/II endometrial carcinoma.

Symptom	Frequency
Pain	44.4%
<i>Abdominal</i>	22.2%
<i>Pelvic</i>	16.7%
<i>Back</i>	5.6%
Bleeding	22.2%
<i>Rectal</i>	16.7%
<i>Vaginal</i>	5.6%

Table 3

Results of univariate analysis of prognostic factors for progression-free survival and overall survival after salvage therapy for pelvic or abdominal recurrence after treatment for Stage I/II endometrial carcinoma.

Prognostic Factors	Progression-Free Survival p-value	Overall Survival p-value
Initial tumor size	0.65	0.30
Initial tumor grade	0.70	0.73
Initial tumor histology	0.51	0.85
Adjuvant RT	0.73	0.46
Adjuvant Chemo	0.19	0.39
Age at recurrence < 65 years 65 years	0.89	0.08
Symptoms at recurrence	0.04	0.10
Time to recurrence	0.89	0.90
Recurrence size 4 cm > 4 cm	0.07	0.16
Recurrence location Regional LN only Other organs	<0.01	0.18
Salvage RT	0.18	0.63
Salvage RT boost	0.46	0.78
Salvage Chemo	0.78	0.55
Salvage Surgery	0.84	0.26

RT = radiation therapy. LN = lymph node.