Original Article

Effect of Adjuvant Therapy on Oncologic Outcomes of Surgically Approved Stage I Uterine Carcinosarcoma: Turkish Gynecologic Oncology Study

Kimyon Cömert et al. Stage I Uterine Carcinosarcoma

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Background: Uterine carcinosarcoma (UCS) is rare neoplasm that mostly presents as metastatic disease. Stage is one of the most important prognostic factor, however, the management of the early stage UCS is still controversial.
Aims: To evaluate prognostic factors, treatment options, and survival outcomes in patients with surgically approved stage I UCS.
Study Design: Cross-sectional study
Methods: Data of 278 patients with UCS obtained from four gynecologic oncology centers were reviewed, and 70 patients with approved stage I UCS after comprehensive staging surgery were studied.
Results: The median age of the entire cohort was 65 years (range; 39–82). All patients underwent both pelvic and paraaortic lymphadenectomy. Forty-one patients received adjuvant therapy. The median follow-up time was 24 months (range; 1–129). Nineteen (27.1%) patients had disease failure. The 3-year disease-free survival (DFS) and cancer-specific survival (CSS) of the entire cohort was 67% and 86%, respectively. In the univariate analysis, only age was significantly associated with DFS (p=0.022). There was no statistical significance for DFS between observation and receiving any type of adjuvant therapy following staging surgery. Advanced age (<75 vs. ≥75 years) was the only independent prognostic factor for recurrence (hazard ratio: 3.8, 95% CI=1.10–13.14, p=0.035) in multivariate analysis. None of the factors were significantly associated with CSS.
Conclusion: Advanced age was the only independent factor for DFS in stage I UCS. Performing any adjuvant therapy following comprehensive lymphadenectomy was not related to the improved survival of the stage I disease.
Keywords: Carcinosarcoma, lymphadenectomy, stage, therapy, uterus

Uterine carcinosarcoma (UCS) is a rare uterine neoplasm, with an incidence of 3–4% among all uterine malignancies [1]. UCS is associated with high risks for metastatic disease at presentation, recurrence, and poor survival [1-3]. Pathologic stage is the most important predictive factor for survival, but the recurrence rate is high, even in the early stages of the disease [2, 4]. The incidence of stage I and II disease is 35–40% [5, 6]. Definitive staging surgery that includes complete lymphadenectomy is recommended as a maintenance treatment for early-stage UCS [1, 6-8]. Furthermore, the survival benefit of lymphadenectomy increases with increasing removed lymph node counts [8]. However, controversial results exist regarding the necessity and the type of

adjuvant therapy in the presence of high-quality lymphadenectomy [5, 6, 9-11]. Adjuvant radiotherapy likely improves local control but has no significant effect on survival for early-stage UCS [11, 12]. Although utilization of adjuvant chemotherapy and chemo-radiotherapy has investigated more frequent because of the tendency of distant recurrence in UCS, even with early-stage disease [6], the optimal postoperative management is still controversial in the early stage.

The survival rates are lower in stage II UCS, but patients with cervical invasion have not been excluded in the majority of the reports related to early-stage UCS [6, 9, 12-14]. Additionally, some of these studies have also included patients who had no comprehensive surgical staging, including lymphadenectomy. Therefore, the main aim of the current investigation is to evaluate the prognostic factors, treatment options, and survival outcomes in patients with only surgically approved stage I UCS to minimize the factors that can affect the survival.

Materials and Methods

The data of patients who underwent at least total abdominal hysterectomy and bilateral salpingo-oophorectomy, and whose definitive pathology report revealed uterine carcinosarcoma between January 1993 and March 2017, were obtained from four gynecologic oncology centers, retrospectively. All patients signed an informed consent that allows the participating institution to use their clinical data. Institutional review board approval was obtained before the study.

All surgeries were performed by gynecologic oncologists, and all pathologies were reported by pathologists specialized in gynecologic oncology at each institution. Records of a total 278 patients who had a pathologic report of UCS were evaluated. The absence of comprehensive lymphadenectomy, having stage II and above disease, and presence of synchronized tumors were the exclusion criteria of the study. Finally, the study included 70 patients with surgically approved stage I UCS (25%).

Staging surgery standardly involves a total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic-paraaortic lymphadenectomy, omentectomy, and cytologic sampling. Lymphadenectomy was performed by skeletonizing both pelvic and paraaortic regions. The upper limit of paraaortic lymphadenectomy was the left renal vein. Patients were staged according to FIGO 2009 surgical staging criteria of UCS. Tumor size was defined as the largest diameter of the tumor. Adjuvant therapy was decided by the gynecologic oncology counsel. Adjuvant chemotherapy was categorized as a paclitaxel-based and non-paclitaxel-based chemotherapy.

Patients who had a complete clinical response to initial treatment were followed up quarterly in the first 2 years, semi-annually up to 5 years, and annually after that. Pelvic examination, abdominal-pelvic ultrasonography, and yearly chest X-ray, unless there was a clinical suspicion, were performed in the follow-up. Thoracic and/or abdominal tomography was used when needed. Disease recurrence during follow-up of patients whose routine evaluations showed the absence of the disease at the first month after initial treatment was accepted as a recurrence. Progressive disease and recurrence were handled as a disease failure after initial therapy. Disease-free survival (DFS) was defined as the time from initial surgery to the failure of disease or last contact. The period from initial surgery to death, because of the disease, or the last visit was defined as cancer-specific survival (CSS). We defined recurrence distal to the pelvic inlet as pelvic recurrence, between the pelvic inlet and diaphragm as abdominal recurrence, and the rest of recurrences as extra-abdominal recurrence. Recurrence in the liver parenchyma, skin, and bone was accepted as extra-abdominal recurrence.

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were expressed as mean ± standard deviation (SD) or median (min–max) for continuous variables and number/percentage for categorical variables. Categorical variables were compared by using the chi-square or Fisher's exact test, as appropriate. The Kaplan–Meier method was used for the assessment of survival outcomes. Survival curves were compared using the log-rank test. Variables with a p-value <0.25 in univariate analysis were selected to evaluate the correlation among variables. After the factors which were not inter-related were determined, a model of recurrence was established for multivariate analysis. Multivariate analysis was performed using a Cox proportional hazards model. The level of statistical significance was set at $p<0.05$.

Results

The median age of the entire cohort was 65 years (range; 39–82). All patients underwent both pelvic and paraaortic lymphadenectomy. The median number of removed lymph node counts was 44 (range; 5–120). Fifty-nine percent of patients had stage 1A disease. Lymphovascular space invasion (LVSI) was determined in 29% of patients. Forty-one (58.6%) patients received adjuvant therapy. The clinical-pathological findings are shown in Table 1.

Adjuvant therapy was performed as only chemotherapy in 22 patients, only radiotherapy in 8 patients, and chemotherapy with radiotherapy in 11 patients. All patients in the paclitaxel-based chemotherapy group (n: 22) received the paclitaxel and carboplatin protocol. Performed protocols for the non-paclitaxel chemotherapy group

are detailed in Table 1. Stage distribution did not significantly differ between groups with and without adjuvant therapy (*p=0.319*).

The median follow-up was 24 months, ranging from 1 to 129 months. Nineteen (27.1%) patients had disease failure. Four patients had disease failure as a progressive disease, and 15 patients experienced recurrence. Among the recurrent patients, recurrence localizations included the pelvic area in 33%, abdominal area in 40%, and the extra-abdominal area in 47%. Only pelvic, only abdominal, and only extra-abdominal recurrences were 13.3%, 20%, and 26.6%, respectively. The most common involved organ in recurrence was the lung (50%). Pelvic recurrence developed in 11% of patients who did not receive adjuvant radiotherapy (observation or only chemotherapy), whereas, none of the patients who underwent radiotherapy had a local recurrence (*p=0.310*). Extra-pelvic recurrence was 13% and 23.5% in patients who received chemotherapy (with or without radiotherapy) and was managed without chemotherapy (observed or underwent radiotherapy only), respectively (*p=0.346*). A total 87.5% of patients with extra-abdominal recurrence did not receive chemotherapy.

The 3- and 5-year DFS were 67% and 55%, and the 3- and 5-year CSS of the entire cohort were 86% and 77%; respectively. In the univariate analysis; only age was significantly associated with DFS (*p=0.022*), and DFS decreased with increase in age. Menopausal status (premenopausal *vs*. postmenopausal), tumor diameter (≤50 mm *vs*. >50 mm*)*, stage (1B *vs*. 1A), LVSI (negative *vs*. positive), number of removed lymph node (≤44 *vs*. >44), and recurrence localization (pelvic *vs*. extra-pelvic) were not significantly associated with DFS. There was no statistical significance for DFS between observation and receiving adjuvant therapy following staging surgery. None of the adjuvant therapies improved DFS when compared with either observation or each other. Paclitaxel-based chemotherapy, with or without radiotherapy, compared to observation or non-chemotherapy options (observation or only radiotherapy) had both 22% improvement in DFS; these differences trended towards statistical significance (*p=0.079* and *p=0.070*, respectively). Among the patients who received only adjuvant chemotherapy; although there was a 23% improvement for DFS in the paclitaxel-based chemotherapy group than non-paclitaxel-based ones, the difference did not achieve statistical significance (86% *vs*. 63%, *p=0.126*). None of the factors were significantly associated with CSS. The survival results are detailed in Table 2.

In stage IA group, there were no statistically significant improvements between observation and any adjuvant therapy or between adjuvant chemotherapy and other options without chemotherapy, for both DFS (3-year; 70% *vs*. 80% or 75% *vs*. 75%, *p>0.05*) and CSS (3-year; 88% *vs*. 87% or 83% *vs*. 91%, *p>0.05*). Stage IA disease detailed as the endometrium confined disease and having myometrial invasion less than half. Six patients with stage IA were excluded because of the absence of the data regarding involvement exceeding the endometrium or not. Five patients had disease confined to the endometrium. Both 3-year DFS and CSS were 100% for patients with disease confined to the endometrium, whereas these values were 75% and 91% at the presence of myometrial invasion in stage IA (*p=0.375* and *p=0.594*, respectively).

The model of multivariate analysis for DFS included stage (stage IB *vs*. stage IA disease), treatment (observation *vs*. paclitaxel-based chemotherapy ± radiotherapy) and age (≥75 years vs. <75 years) (Table 3). According to multivariate analysis, age was related to a statistically significant hazard ratio for a recurrence of 3.8 *(*95% CI=1.10–13.14, *p=0.035)*. Advanced age was the only independent factor for recurrence (Fig1).

Discussion

UCS has an aggressive behavior. The 5-year overall survival (OS) ranged from 45% to 65% for early-stage disease [15, 16]. Recurrence rate varied from 30% to 50%, even if stage I disease [2, 7]. In our study, the recurrence rate, 5-year DFS, and 5-year CSS of stage I UCS was 27%, 55%, and 77%, respectively. Similar to previous reports [2, 6, 7, 13], distant recurrence was the most common recurrence type, in our study.

The clinical-pathologic factors that reflect the recurrence and prognosis are not clear in early-stage disease. Deep myometrial invasion [7, 17], LVSI presence [9], tumor size (≥5 cm) [7], history of cancer [9], older age (≥60 years) [7], and sarcoma dominance [7] are asserted as factors associated with worse survival outcomes in uterine-confined carcinosarcoma. Additionally, Leath *et al*. [2] reported that the only type of epithelial component (poorly differentiated endometrioid histology or serous type) was associated with an increased recurrence rate in stage I disease. In our study, advanced age was the only independent factor for DFS in stage I UCS.

Surgery is the cornerstone of UCS therapy [18, 19]. The necessity of adjuvant therapy is considered because of the high recurrence rate and poor survival, even in early-stage UCS. According to our knowledge, only a few studies have investigated stage I UCS, exclusively [2, 6-8, 10, 13]. Leath *et al*. [2] stated a 50% recurrence rate for patients who underwent surgery alone, in stage I UCS. According to this finding, they concluded that observation is not to be considered, even in surgically staged patients. However, that study included a very small sample size, whose lymphadenectomy included pelvic lymphadenectomy and paraaortic sampling, with a median of nine removed lymph nodes [2]. The chemotherapy-containing option, especially as a chemo-radiotherapy, was claimed to be associated with better survival [6, 7, 13]. Nonetheless, results of these studies must be reconsidered before reaching an absolute conclusion due to the low removed lymph node count.

Rauh-Hain *et al*. [6] analyzed the United States National Cancer Database and found that chemotherapy-containing therapy (with or without radiotherapy) was associated with improved survival compared to only surgery, among patients with stage I disease after comprehensive surgical staging. Due to confidentiality of the database information, the technical details and adequacy of surgery could not be detailed in their report. According to Guttmann *et al*. [13], who studied both stage I and stage II UCS, chemo-radiotherapy is associated with a better OS than observation, radiation alone or chemotherapy alone, separately. The chemo-radiotherapy was linked to both improved progression-free survival (PFS) and vaginal recurrence-free survival in comparison with observation, but not with radiotherapy or chemotherapy alone. Independent prognostic factors were determined as adjuvant therapy (all types of therapy *vs*. observation) and lymphadenectomy for OS but only adjuvant therapy for PFS and vaginal recurrence-free survival. Brachytherapy combined regimes (with chemotherapy or external beam radiotherapy) had a lower vaginal recurrence-free survival than those without brachytherapy [13]. This result highlighted the potential to provide local control with low toxicity. In patients with stage I and pathologically-negative nodes, Seagle *et al*. [8] showed that vaginal brachytherapy was accompanied by a better survival, whereas adjuvant chemotherapy had no survival benefit in that cohort.

In an examination of the stage 1 disease, Matsuo *et al*. [7] noted that chemotherapy (with or without radiotherapy) was independently concomitant with improved DFS and OS compared to non-use (observation or radiotherapy), both in stage I and stage IA disease. The study showed that chemotherapy was an independent predictor for both local and distant recurrence. Radiotherapy decreased the local recurrence rates in the presence of risk factors, including high-grade carcinoma, sarcoma dominance, and deep myometrial invasion. Local or distant recurrence did not significantly decrease with radiotherapy or chemotherapy in patients who underwent both pelvic and paraaortic lymphadenectomy. There were no differences in DFS, OS, distant recurrence, and local recurrence risk between chemo-radiotherapy and chemotherapy alone [7]. Contrastingly, Garg *et al*. [10] investigated elderly patients (≥65 years) with stage I UCS but found no significant improvement in survival when adding any adjuvant therapy following surgery. Similar to Garg *et al*. [10], our results also showed that addition of any adjuvant therapy neither improved DFS nor CSS, even despite the relatively younger patients in our study population (median age: 65 years).

The absence of lymphadenectomy was not excluded from the eligible criteria in the trials discussed above [6, 7, 10, 13]. This issue is important in evaluating studies because lymphadenectomy is strongly recommended, based on the presence of up to 33% of occult lymph node metastasis and the high risk of upstaging in clinically apparent uterine-confined disease [17-20]. Local and distant recurrence rates significantly increased in unstaged patients, and OS was approximately 60% in stage I patients who were only observed postoperatively [7]. Lymphadenectomy in the early stages of the disease is affiliated with an improvement in both DFS and OS [8, 17, 18]. Therefore, in our study, the higher survival rate (5-year CSS: 83%) in observed patients (than those in other studies that did not exclude lymphadenectomy) and the absence of significant differences in survival among therapy types can be attributed to the exclusion of patients with no performed lymphadenectomy and a high removed lymph node count (median: 44).

Ifosfamide is accepted as a most active single agent [10]. Nevertheless, combination therapies came to the fore for improved survival. Previous studies have shown a better PFS with the addition of cisplatin to ifosfamide in early-stage disease [16, 21]. Continuation of poor prognosis in UCS reflected the fact that optimal treatment protocol has still not been achieved even if stage I disease. Additionally, the high toxicity rates with limited survival advantage of ifosfamide–cisplatin regimens [21, 22] have led to focusing on changing the chemotherapy procedures. Particularly, carboplatin and paclitaxel regimen has been strongly suggested for, especially, the advanced stage or recurrent disease, attributed to the improved survival rates with negligible toxicity rates [23-26]. The effectiveness of carboplatin–paclitaxel in the early stage is not clear. According to Gutmann *et al*. [13], carboplatin–paclitaxel did not impact survival when compared with other regimens in stage I/II disease. In our study, the majority (67%) of stage I patients who underwent adjuvant chemotherapy received paclitaxel-based chemotherapy (carboplatin–paclitaxel regimen). Among the patients who received only adjuvant chemotherapy; although there was a 23% improvement for DFS in the paclitaxel-based chemotherapy group than non-paclitaxel-based ones, the difference did not achieve statistical significance. Although none of the adjuvant therapies were associated with improved survival in stage I disease, DFS in the carboplatin–paclitaxel, with or without radiotherapy, group trended towards significance relative to options without chemotherapy, in our results. Nonetheless, drawing an unequivocal conclusion is difficult because of the small sample size.

The retrospective study design and small sample size are the main limitations of this study. Data regarding the doses and the machine type of radiotherapy could not be reached from records within 24 years for all cases, since the condition of giving the radiotherapy could not be optimized. Due to the lack of consensus on standardized therapy regimens, subgroup analysis for therapy regimens is performed with a small sample size, which might potentially affect the comparisons. In our study, patients who had approved endometrium-confined disease with comprehensive lymphadenectomy had 100% for both DFS and CSS. This result leads us to think that patients with endometrium-confined disease may be evaluated separately from stage IA patients. However, achieving a definitive result with that small subgroup sample is difficult. It will be important to assess a comparatively larger

sample size with endometrium-confined UCS. In spite of that, this study includes only stage I UCS cases, which were all approved by performing a high-quality, comprehensive lymphadenectomy.
Performing any adjuvant therapy following comprehensive lymphadenectomy was not linked to an improvement in survival of stage I disease. Given the still high recurrence rates in stage I UCS, further studies that include relatively larger sample numbers and a prospective design are needed to investigate the therapy options in stage I UCS or must be focused on new therapeutic approaches. The carboplatin–paclitaxel regimen seems to hold promise, also for the early-stage disease but drawing an accurate conclusion is difficult based on current knowledge.

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Table 1: Clinical-pathological features of entire cohort

Factors		n (%)
Menopausal status	Pre-menopausal	5 (7)
	Post-menopausal	65 (93)
Symptom	Bleeding	65 (92.9)
	Pain	2 (2.9)
	Asymptomatic	2 (2.9)
	NR	1 (1.3)
Stage	1A	41 (59)
	1B	29 (41)
LVSI	Not present	39 (56)
	Present	20 (29)
	NR	11 (15)
Adjuvant therapy	No	29 (41.4)
	Yes	41 (58.6)
Protocol of adjuvant chemotherapy[∞]	Paclitaxel-based[¥]	22 (67)
	Non-paclitaxel chemotherapy	11 (33)
	• Only adriamycin	2
	• Adriamycin + cisplatin	2
	• CAOS	1
	• Cisplatin	1
	• IMA	5
Localization of recurrence	Only pelvic	2 (13.3)
	Only abdominal	3 (20)
	Only extra-abdominal	4 (26.6)
	Pelvic + abdominal	1 (6.7)
	Pelvic + extra-abdominal	1 (6.7)
	Abdominal + extra-abdominal	2 (13.3)
	Pelvic + abdominal + extra-abdominal	1 (6.7)
	NR	1 (6.7)

LVSI: Lympho-vascular space invasion; NR: Not reported; CAOS: Actinomycin-D + Doxorubicin + Vincristine + Cyclophosphamide; IMA: Ifosfamide + Mesna + Adriamycin

[∞] The percentages of this findings calculated among the patients received only chemotherapy (n: 33)

[¥] Paclitaxel-based chemotherapy protocol included paclitaxel and carboplatin for all patients received this regimen.

Table 2: Disease free survival (DFS) and cancer specific survival (CSS) results of entire cohort

Parameters		n	3-year DFS (%)	*p* value	3 year CSS (%)	*p* value
Age1 classification	≤55	13	91	**0.022***	88	0.820
	55-≤75	48	67		86	
	>75	9	43		86	
Age2 classification	<75	60	73	**0.005***	86	0.934
	≥75	10	38		88	
Menopausal status	Premenopausal	5	100	0.169	100	0.356
	Postmenopausal	65	65		85	
Tumor diameter (median, mm)	≤50	26	69	0.797	85	0.526
	50<	25	74		91	
Stage	1A	41	77	0.105	87	0.469
	1B	29	57		85	
Number of removed LN	≤44	32	74	0.388	96	0.149
	44<	31	66		77	
LVSI	Absent	39	70	0.190	87	0.738
	Present	20	67		84	
Adjuvant therapy	Observation	29	61	0.517	83	0.874
	Adjuvant therapy (any)	41	71		89	
	Observation	29	61	0.323	83	0.594
	Only Adjuvant CT	22	75		94	
	Observation	29	61	0.857	83	0.914
	Only Adjuvant RT	8	60		75	
	Observation	29	61	0.834	83	0.782
	Adjuvant CT and RT	11	71		86	
	Only Adjuvant CT	22	75	0.357	94	0.586
	Only Adjuvant RT	8	60		75	
	Only Adjuvant CT	22	75	0.555	94	0.479
	Adjuvant CT and RT	11	72		86	
	Paclitaxel-based chemotherapy[¥]	14	86	0.126	100	0.145
	Non-paclitaxel chemotherapy[¥]	8	63		88	
	Observation	29	61	0.106	83	0.171
	Paclitaxel-based chemotherapy	14	86		100	
	Observation	29	61	**0.079**	83	0.314
	Paclitaxel -based chemotherapy ±RT	22	83		80	
	Observation or RT	37	61	**0.070**	81	0.279
	Paclitaxel -based chemotherapy ±RT	22	83		80	
Localization of recurrence	Pelvic	2	-	-	100	0.964
	Extra-pelvic	12	-		55	
Presence of extra-abdominal recurrence	No	6	-	-	67	0.947
	Yes	8	-		58	

[¥] Among the patients who received only adjuvant chemotherapy (n: 22)
LN: lymph node; CT: Chemotherapy; RT: Radiotherapy
**p<0.05 is statistically significant.*

Table 3. Multivariate analysis of stage I uterine carcinosarcoma for recurrence

	Hazard Ratio (95% CI)	***p* value**
Model		
Stage (*IB vs. IA*)	1.5 (0.44- 5.25)	0.496
Age (*≥75 years vs. <75 years*)	3.8 (1.10-13.14)	**0.035***
Treatment (*Observation vs. Paclitaxel-based chemotherapy ±RT*)	3.2 (0.70-15.3)	0.132
*p <0.05 is statistically significant.		

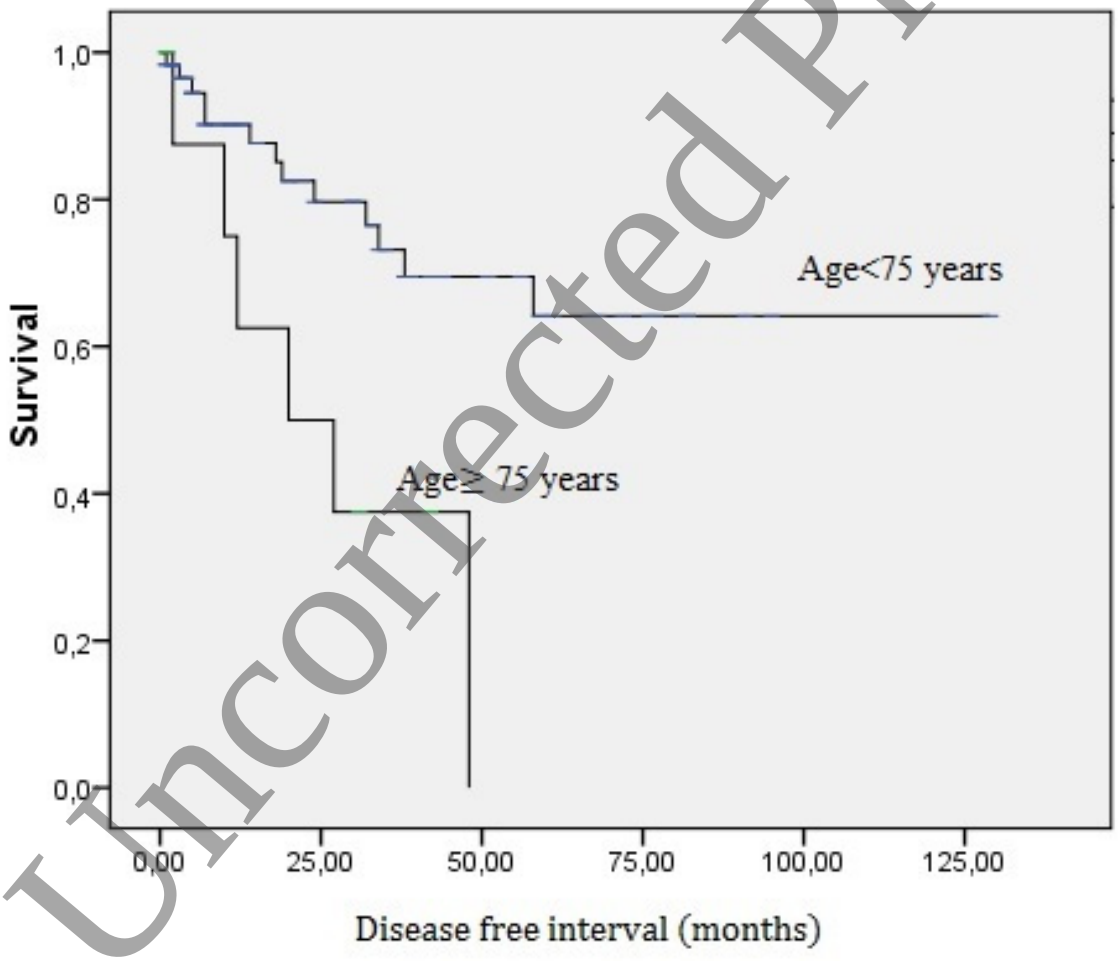

Fig1: Disease free survival decreased with increase in age.