Journal of Diseases
2015 Vol.2, No.1, pp.1-11
ISSN(e): 2410-6550
ISSN(p): 2413-838X
DOI: 10.18488/journal.99/2015.2.1/99.1.1.11

RE-IRRADIATION FOR RECURRENT HEAD AND NECK SQUAMOUS CELL CARCINOMA AFTER PRIMARY RADICAL THERAPY

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ABSTRACT

Introduction: Loco-regional failures, recurrence or second primary after radiotherapy (RT) is a significant problem in head and neck cancer (HNC) and represent a challenge. Methods: 39 patients were referred to the Radiation Oncology Department, A. C. Camargo Cancer Center, Sao Paulo, Brazil between 2007 to 2012 to have a second new course of RT (Re-RT) to a previous irradiated area in the head and neck. Results: Median age of patients was 53.8 (range, 31-74) years. Twenty four (61.5%) patients had surgery and Re-RT. The first radiation course dose ranged from 45 Gy to 72 Gy (median 60.0 Gy) and the median interval between the initial and second radiation course was 32 (range, 9-146) months. The median follow-up was 2.6 (range, 0.5-5.9) years. The 2- and 5-year actuarial OS, PFS and LC rates were 76.0%, 38.6%, 83.8%, 75.0%, 27.0% and 14.0%, respectively. Re-RT with IMRT when compared to other techniques showed PFS and LC advantages, p= 0.018 and p=0.019, respectively, confirmed by Cox regression multivariate - HR=6.08 (p= 0.020, 95% CI: 1.331- 27.767). Major toxicity occurred in 14 (35.9%) patients and eye observed no carotid artery blowout in this series. Conclusion: Re-RT should be offered for patients who are not suitable for surgery or for those with marginal resections, with a clear understanding that survival is poor and many of these patients will suffer severe radiation-related insults to their quality of life, during and after treatment.

Keywords: Squamous cell, Head neck cancer, Radiotherapy, Re-irradiation, Salvage therapy, Conformal radiation, Intensity modulated radiation.

Contribution/ Originality

This study contributes in the existing literature by analyzing the impact of new technologies in the local control of recurrent head and neck cancer

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1. INTRODUCTION

Loco-regional failures, recurrence or second primary after curative radiotherapy (RT) alone or in combination with surgery and/or chemotherapy (CHT) is a significant problem in head and neck cancer (HNC) and represent a challenge. In Brazil, for 2014, it is expected 15,290 new diagnoses of oral cavity cancer and around 70% of these new diagnoses will probably have a course of radiation therapy as part of their definitive treatment [1].

For those patients who present with local or loco-regional failure (Re-HNC) after primary radiotherapy (RT), re-irradiation (Re-RT) is generally not considered as the first line salvage therapy. Surgical re-resection, in this situation, is often impossible or inadequate due to the intimate anatomic relation between disease and critical structures, making Re-HNC a poor prognosis disease [2].

Salvage therapy for Re-HNC is a controversy issue with best management still to be defined. Complete surgical resection was historically the only curative option for Re-HNC, as the initial treatment course substantially impacts and reduces the flexibility and intensity of re-treatment, especially in terms of a new radiation course. Otherwise, the prognosis of patients with Re-HNC is grim if the tumor is left untreated, with a median survival of only 5 months [3-5]. Chemotherapy (CHT) alone, in this setting, is also associated with poor median survival rates with no chance of long-term control, despite new drugs available [6, 7].

Potentially curative approaches for Re-HNC include definitive surgery with or without adjuvant Re-RT, given by external beam or brachytherapy [8]. Data form the literature have shown that maximum debulking surgery combined with Re-RT can lead to a better local control (LC) when compared to surgery alone [3]. Conversely, a new second course of RT for recurrent disease is always a problem and of limited feasibility, because of the difficulty to spare adjacent normal tissues, resulting in undesirable late effects on the salivary glands, mandible, and muscles of mastication.

Two different modalities of RT can be used in the setting of Re-RT: the use of intra-operative interstitial implantation that is suited to deliver a high dose to a limited volume, called brachytherapy or external beam RT, usually delivered using either tri-dimensional conformal (3D-CRT) or intensity-modulated RT (IMRT). The last one allows for dose-escalation to a wider or smaller volume, while minimizing normal tissue toxicity [9, 10].

Many reports have suggested that Re-RT concomitantly with CHT is feasible for curative or palliative intent. The combination of both treatments, with or without a surgical resection associated, may achieve long-term disease control in some patients, but at the expense of increasing rates of late toxicities [10-15].

2. METHODS

A total of 39 patients were referred to the Radiation Oncology Department, A. C. Camargo Cancer Center, Sao Paulo, Brazil between 2007 to 2012 for Re-RT as part of a curative treatment.

The study was performed under an Institutional Review Board-approved retrospective chart review data analysis.

All patients were initially evaluated by a multimodality treatment team, comprising an otolaryngologist or head and neck surgeon, medical oncologist, and radiation oncologist.

Histological confirmation of malignancy was required before initiating the re-treatment, for all patients who were not candidates or who refused a surgical resection. A detailed physical examination, including flexible nasopharyngolaryngoscopy, neck computed tomography (CT) and or magnetic resonance imaging (MR) were mandatory. Positron emission tomography (PET) or PET-CT was performed in 17 (43.5%) patients.

Clinical characteristics of patients and tumor are shown in table 1.

Fourteen patients (35.9%) patients did not have surgery as part of their salvage treatment as follows: 11 (28.2%) patients were not candidates for surgical procedure due to extent of disease, whereas 3 (7.7%) refused surgery.

Concurrent CHT was indicated in 27 (69.2%) patients, typically with a platinum-based regimen.

Re-RT was delivered using IMRT for 24 (61.5%) patients. Twelve (30.7%) patients had 3D-CRT and only 3 (8.0%) patients had conventional treatment plans.

The clinical target volume included areas of macroscopic and or microscopic disease in all patients and elective neck irradiation was not performed. The primary avoidance structures in the Re-RT plan were the spinal cord and brain steam.

The goals of inverse planning were to ensure homogenous coverage of the area of interest and limit the additional spinal cord dose or brain steam to a dose of up to 8-10Gy.

Acute and late toxicities were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Acute and late toxicity were grouped together, as minor or major complications. Minor complications were those managed with conservative and outpatient measures. Major complications were those that required hospital admission or in-hospital intervention (eg: gastrostomy feeding-tube placement, tracheostomy, laser therapeutic interventions).

2.1. Statistical Methods

The follow-up was measured from the first day of Re-RT of the day of death or the last clinic visit before analysis. Actuarial estimates of local and regional progression-free survival (PFS), local control (LC) and overall survival (OS) were calculated using Kaplan-Meier estimates. Breslow's test was used to compare differences in survival estimates because it is more powerful when the hazard functions are not parallel, giving more weight to early failures. Cox proportional hazard model was used to examine the effect of the time between the first and the second radiation courses on survival. All significant tests were two-sided, and statistical significance was accepted for a calculated p value <0.05.

3. RESULTS

Median age of patients was 53.8 (range, 31-74) years. Twenty four (61.5%) patients had surgery and Re-RT. Eleven (28.2%) patients had partial resections, 7 (17.9%) microscopic positive margins (tumor less than 1 mm of the inked margin) and 4 (10.2%) macroscopic (gross tumor in the inked margin) positive margin.

The dose given in the first radiation course ranged from 45 Gy to 72 Gy (median 60.0 Gy). The median interval between the initial and Re-RT course was 32 (range, 9-146) months. The median cumulative dose delivered in both RT courses was 115.7 (range,90-140) Gy, as shown in table 2.

Six (15.3%) patients received less than 50 Gy in the Re-RT course because of acute toxicity or total radiation dose given in the first treatment. Twenty two (56.4%) patients received between 50–59 Gy and 11 (28.2%) received more than 60 Gy in the Re-RT course. The median overall treatment time of the Re-RT was 30 (range, 22-46) days.

At a median follow-up of 2.6 (range, 0.5-5.9) years there were 15 (38.4%) patients dead. Six (15.4%) patients died due local disease progression, 5 (12.8%) because of distant metastasis and 4 (10.2%) due other causes. At the time of this analysis there were 24 (61.5%) patients alive and 16 (41.0%) disease free.

The 2- and 5-year actuarial OS, PFS and LC rates were 76.0%, 38.6%, 83.8%, 75.0%, 27.0% and 14.0%, respectively (Figures 1,2 and 3).

Univariate statistical analysis is shown in table 3. There was no statistically significant difference on median Re-RT doses among patients who had local failure and who were disease free, p=0.518. Concurrent CHT to Re-RT was not associated with neither PFS (p=0.929) nor LC (p=0.178). Conversely, the nodal stage at time of salvage associated with PFS (p<0.001) and IMRT when compared to other techniques showed PFS and LC advantages, p= 0.018 and p=0.019, respectively. Figure 4. Cox regression multivariate analysis confirmed that patients who underwent Re-RT with techniques other than IMRT had an inferior PFS, HR=6.08 (p= 0.020, 95% CI: 1.331- 27.767).

Five (12.8%) patients had distant metastasis. Two of them had both local recurrence and distant failure. The sites of distant metastasis included lung, brain and bones.

Major toxicity occurred in 14 (35.9%) patients, as follows: 3 (7.6%) patients had pharyngeal strictures, 4 (10.2%) patients had severe neck fibrosis and 7 (17.9%) patients were tracheotomy-dependents as result of the salvage therapy. We observed no carotid artery blowout in this series.

4. DISCUSSION

The management of Re-HNC is one of the most challenging procedures in oncology. Surgical re-resection is often impossible or inadequate due to the intimate anatomic relation between disease and critical structures, with complications unacceptable to the patient, making the recurrent or second primary HNC a very poor prognosis disease. CHT in the setting of

unresectable local or regional recurrence is associated with a median survival of 5–6 months, with no chance of long-term control, despite new drugs available [5, 6]. Re-RT is generally not considered as the first line approach for managing Re-HNC [2] and when evaluating the published data it is important to emphasize the difficulty to compare results across different Re-RT series, because outcomes vary substantially based upon patient selection, treatment technique, and the differentiation between curative or palliative intent of the treatment.

In the literature the 5-year survival rates for Re-HNC varies from 13% in unselected series to 93% in highly selected series [16-18]. The results of Re-RT based on conventional and less sophisticated plans are disappointing and relatively scarce in the literature. Goldstein, et al. [18] reported that the 1-year survival rate was 23.0% and 46.3% for patients treated with palliative and curative treatments. The strength of our series is that it is relatively recent, involves operable and inoperable patients who had Re-RT only for non-metastatic HNC, treated with curative intent using more sophisticated techniques.

Dose given in a Re-RT is probably an important issue related to tumor control. It has been noted that patients who received more than 58 Gy in the Re-RT course tend to have a better LC and OS [2, 19]. In our study the 5-year actuarial OS rate was 38.6%, but conversely to these results, we did not observe a statistical significant difference in LC related to the dose given, probably due to the relative small number of patients in our series.

Surgical resection of Re-HNC is an important factor related to LC confirmed in our analysis, but conversely to our results, Biagioli, et al. [20] did not confirm this in 20 (27%) of 74 patients who underwent salvage surgical resection prior to Re-RT.

The use of IMRT in recent years resulted in improvements in dose conformability around the targets when compared to 3D-CRT and other techniques. IMRT for Re-RT in our study was the only predictive factor for PFS when compared to other techniques, confirming the potential benefit from full-dose Re-RT. The impact of the technique used for Re-RT was also reviewed by Popovtzer, et al. [21], but conversely to our results, they could not find any statically significant difference in terms the results between both techniques. This may be explained by the shorter follow-up of the patients who were treated with IMRT when compared to our results.

Concurrent CHT along with Re-RT is paralleled to its use in the primary setting, and the goal is to increase LC and OS. Concurrent CHT was not a statistically significant factor associated with PFS (p=0.330) in our study, probably due to the small number of patients who had such combination of treatment.

The complications rate relate to Re-RT vary in published studies, probably as a result of the length of survival and type of treatment employed. In our series, adverse events occurred relatively frequently, even in patients who did not have concurrent CHT. One explanation for our relatively high rate of radiation-related toxicities is grouping of acute and late toxicity. We think this is an appropriate approach in a population of patients for whom survival is likely to be short, and that any radiation-related toxicity is likely to have a detrimental effect on the quality of life.

We noted that despite the high incidence of toxicity in observed in our analysis, there was no relation between presence of concurrent CHT to Re-RT (p=0.929) and increased incidence of complications. Late toxicity was acceptable in our series, although it was clearly increased by comparison with the first RT course.

It is important to note that despite an absence of statistically significant difference in the results among the patients treated with multimodality therapy in our analysis, the combination of surgery and Re-RT with or without, concurrent CHT, are the best option for salvage therapy. Salama, et al. [12] confirmed this as an independent prognostic factor for OS and LC when evaluating a subset of 115 previously irradiated patients.

Re-RT in adjuvant setting, when a salvage complete resection is performed is still motive of debate. Although our results do not support the routine use of adjuvant Re-RT in this situation, we think prospective studies are still needed to clarify the role of Re-RT in circumstances such as close surgical margins (< 1 mm), where the risk of local new recurrence is relative high.

5. CONCLUSION

Despite the small size of the sample in this study, not permitting to draw any definitive conclusion, complete resection or debulking surgery should be encouraged for all patients presenting with recurrent or second HNC previously irradiated. Re-RT should be offered for patients who are not suitable for surgery or for those with marginal resections, with a clear understanding that survival is poor and many of these patients will suffer severe radiation-related insults to their quality of life, during and after treatment. The real potential of CHT is this setting is still to be defined.

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Table-1. Patients charactheristics

Variable		**N**	**%**
Age	≤ 65	21	53.9
	> 65	18	46.1
Gender	male	27	69,2
	female	12	30,8
Initial Tumor Stage	0	6	15,4
	1	7	17,9
	2	16	41,0
	3	6	15,4
	9	4	10,3
Initial Lymphonode Stage	0	12	30,8
	1	4	10,3
	2	17	43,6
	3	6	15,4
First RT Course - Technique	other	4	10,3
	2d	20	51,3
	3d	15	38,5
Recurrent Tumor stage*	0	16	41,0
	2	15	38,4
	3	4	10,3
	4	4	10,3
Recurrent Node stage*	0	21	53,9
	1	6	15,4
	2	10	25,6
	3	2	5,1
Surgery	No	14	35.9
	yes	25	64,1
Re-RT – technique*	imrt	15	64,1
	2D	2	5.1
	3D	12	30.8
ReRT combined CHT	Yes	27	69.2
	No	12	30.8

* at the time of Re-RT
Legend – Re-RT – re-irradiation, CHT – chemotherapy

Table-2. Irradiation doses at first course and re-irradiation course

	Fisrt RT (Gy)	**Re-irradiation (Gy)**
Mean	58.7	55.2
Median	60.0	55.5
Minimum	45.0	30.0
Maximum	72.0	70.4

Table-3. Univariate analisys for PFS and LC

			PFS			**LC**		
Variable		**N**	**Censored**	**%**	**p**	**Censored**	**%**	**p**
Tumor Stage *	0	16	4	25.0	<0.001	4	27.0	<0.001
	1	15	12	80.0		13	86.6	
	2	4	4	100.0		4	0	
	3	4	4	100.0		4	0	
Node Stage*	0	21	10	47.6	<0.001	11	52.3	0.002
	1	6	6	100.0		3	50.0	
	2	10	6	60.0		9	90.0	
	3	2	2	100.0		2	100.o	
RRT combined to any CHT modality	No	8	6	75.0	0.314	6	75.0	0.697
	Yes	31	18	58.1		19	61.2	
Re-RT combined to Surgery	No	14	11	78.6	0.051	11	78.6	0.090
	Yes	25	13	52.0		14	56.0	
Surgical Margin	free	14	8	57,1	0.236	7	50.0	0.281
	micro	7	5	71,4		5	71.4	
	spic	4	2	50,0		2	50.0	
	+ macro scopic + no surgery	14	9	64,3		11	78.5	
Neoadjuvant CHT to Re-RT	No	33	20	60,6	0.154	22	66.7	0.519
	Yes	6	4	66,7		3	50.0	
Concurrent CHT to Re-RT	No	13	9	69,2	0.372	8	88.9	0.179
	Yes	26	15	57,7		17	65.4	
Age (years)	≤ 65	21	8	38,1	0.040	10	47.6	0.020
	> 65	18	16	88,9		15	83.3	
Tumor patological Stage*	rT0-2	31	18	58,1	0.096	20	64.5	0.152
	rT3-4	8	6	75,0		5	75.0	
Re-RT technique	IMRT	25	11	44.0	0.005	11	44.0	<0.001
	Other	14	13	92,9		14	0	
Elective node Re-RT	No	25	14	56,0	0.272	14	56,0	0.147
	Yes	14	10	71,4		11	78.5	
Neck only Re-RT	No	21	12	57,1	0.371	10	83.3	0.572
	Yes	18	12	66,7		15	83.3	
Disease Free Interval (months)	≤ 36	19	14	73.6	<0.001	19	100.0	0.001
	> 36	20	10	50.0		6	30.0	

* at recurrence

Legend – Re-RT – re-irradiation, CHT – chemotherapy

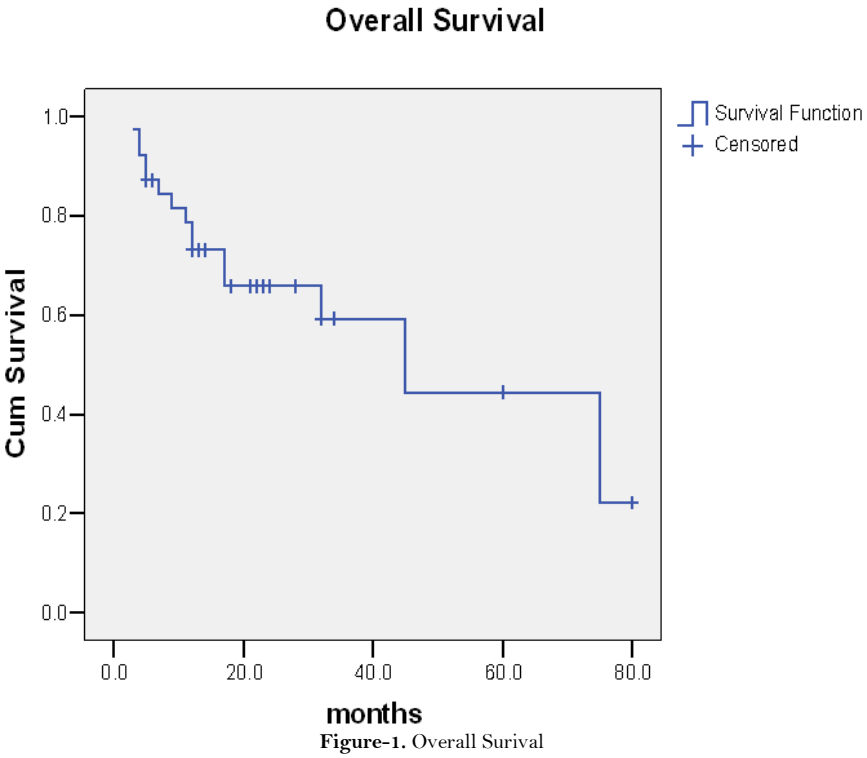

Figure-1. Overall Surival

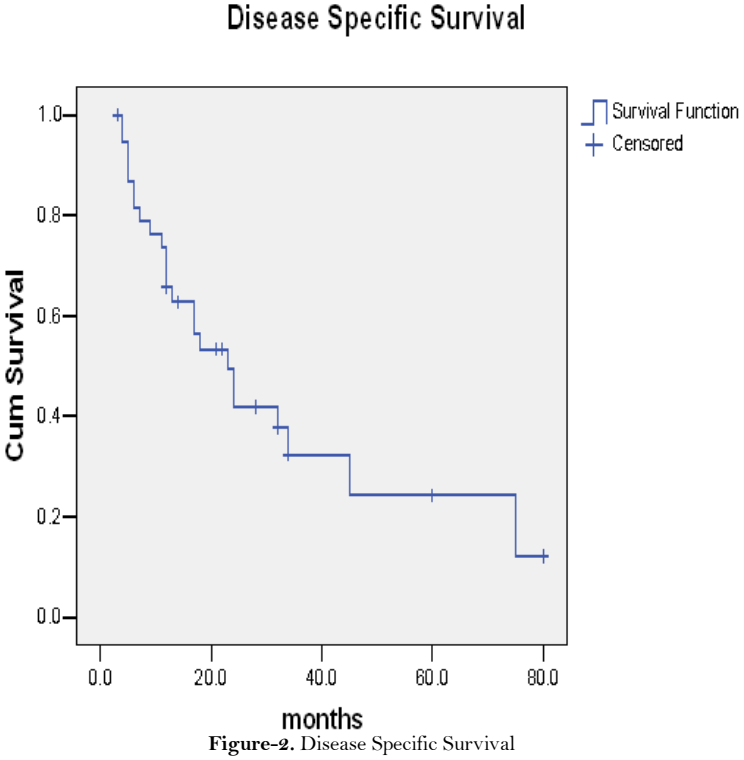

Figure-2. Disease Specific Survival

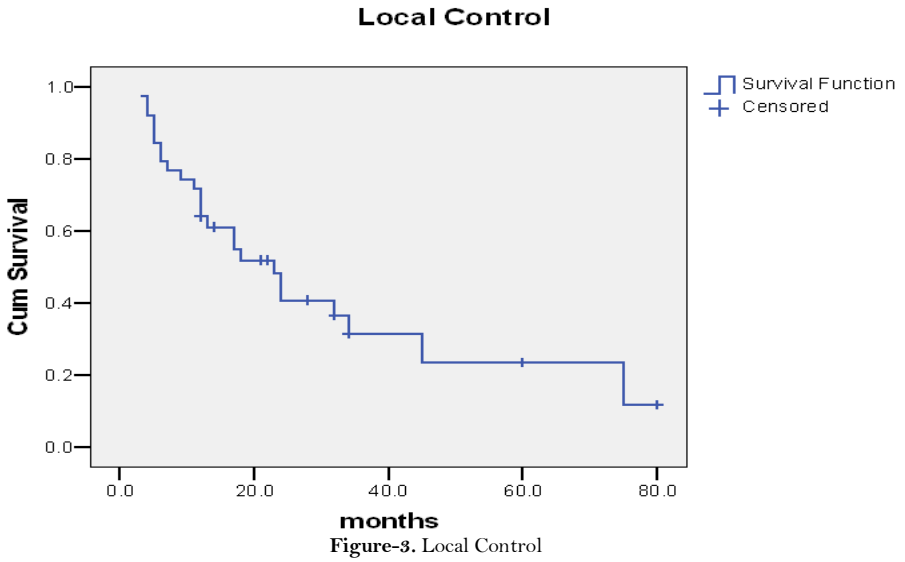

Figure-3. Local Control

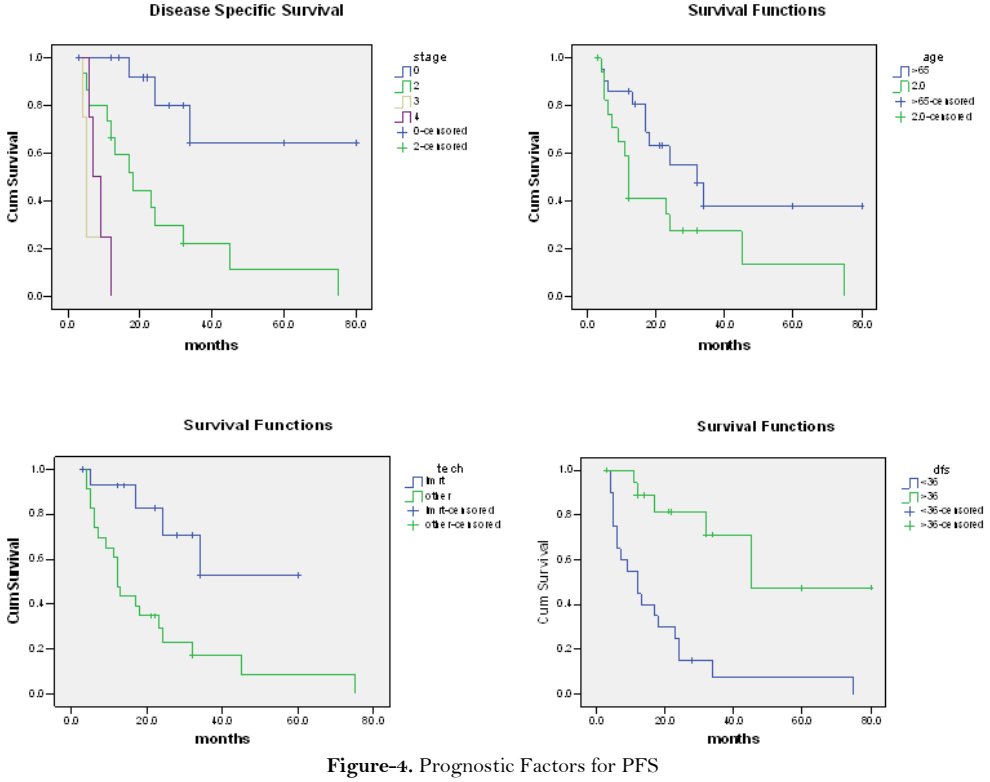

Figure-4. Prognostic Factors for PFS