NACT followed by surgery in advanced oral squamous cell carcinoma: Pathological response as a prognostic indicator?

Abstract:

Objective: **To analyze the pathological response and clinical outcomes in patients receiving NACT followed by surgery in locally advanced oral squamous cell carcinoma (OSCC).**

Methods: Retrospective study of prospectively collected data of 87 patients who received NACT followed by surgery in locally advanced oral squamous cell carcinoma (OSCC) from 2018 to 2021 was done in the department of head and neck surgery. The pathological response to NACT was assessed and classified into complete response, partial response and no response. Pathological response and its prognostic importance with various parameters was evaluated.

Result: Total number of 87 patients received NACT followed by surgery for locally advanced oral squamous cell carcinoma (OSCC), 58 cases were of buccoalveolar complex, 27 were of tongue and 2 were of MOU, complete response to NACT was seen in 4 tongue and 2 buccoalveolar complex and 2 MOU cases, partial response to NACT was seen in 35 buccoalveolar complex and 11 tongue cases. Out of total 87 patients 25 patients defaulted adjuvant therapy and did not completed prescribed treatment and were lost to follow up. 62 patients who completed treatment and follow up, 38 (61.2%) patients were present in the complete (6) and partial response (32) group, rest (24) in no response group. In the median follow up period of 42 months, the complete and partial response group patients showed better overall survival (OS) (P = 0.058) and disease-free survival (DFS) (P = 0.174) then the no response group (OS)(P = 0.058) and (DFS) (P = 0.174) but statistically no significant changes amongst group were observed.

Conclusion: In complete response group tongue lesion shows better response than buccoavleolar complex lesion. Complete response group shows better DFS and OS than no response group.

Key words: oral squamous cell carcinoma, neoadjuvant chemotherapy, pathological response

Introduction:

Multimodality treatment is the standard of care for resectable locally advanced oral squamous cell carcinoma (OSCC) [(1)]. In very advanced / borderline resectable cases NACT has shown to down stage the disease, making it resectable with reduced

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morbidity, better quality of life as well as improvement in overall survival and local control.

Concept of NACT first introduced by licitra in resectable OSCC in 2003, this trial has not shown any significant benefit in overall survival and locoregional control, madibular preservation was seen in around 21% of patients and reduced distant metastasis noticed so NACT used as treatment modality in resectable oral cancer only in case of clinical trial, as upfront surgery is treatment of choice[2].

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In literature NACT has shown promising result in borderline resectable cases with significant improvement in overall survival and local control as R0 resection become possible in advanced oral squamous cell carcinoma (OSCC). Patil et al noticed in 43% of patient tumor downsized and R0 resection achieved and improved overall survival as compared to non surgical treatment[3, 4].

According to various meta analysis, the positive response to NACT in advanced OSCC is related to better survival [5–7]. In individuals with locally advanced OSCC, NACT may lower the risk of distant metastases and fair disease control.

Role of NACT in case of unresectable OSCC limited data available, reduction in distant metastasis is noticed apart from it any other benefit is controversial as compared to upfront chemoradiation, as in unresectable cases reduction in tumor size hardly matters.

To summarize NACT for resectable OSCC has been the subject of numerous researches; however none have been able to show a meaningful increase in locoregional control or overall survival [8–10]. Therefore, more research is required to understand the pathological pattern of tumour response after NACT and to identify a biomarker for identifying OSCC cases with a fair response.

While in borderline resectable cases with locally advanced disease where an appropriate surgical margin is not attainable, NACT is primarily taken into consideration. In order to increase the likelihood of survival, a therapeutic strategy for patients who did not respond well to NACT should also be created.

Typically, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria are used to classify NACT responses [11]. The size of the lesion on imaging is the foundation of the RECIST criteria. But there are no standard criteria for pathological evaluation of response to NACT and its implication on survival.

Material and methods:

The objective of study is to evaluate:

1. The pathological response to NACT in advance OSCC cases.

2. To asses minimum 18 months overall survival (OS) from date of completion of treatment till end of study.

3. To asses disease free survival (DFS) from date of completion of treatment till the last known recurrence.

Participants and study design:

The clinical data of 87 OSCC patients receiving NACT followed by surgery in locally advanced oral squamous cell carcinoma (OSCC) from January 2018 to April 2021 at Kailash Cancer Center were reviewed for this retrospective analysis. This study was approved by the institutional review board (IRB), and all participants signed an informed consent agreement. Patients details and other variables were collected from hospital database.

The pretreatment evaluation comprises of the patient's medical history, physical examination, performance status, serum biochemical profiles, complete blood cell count, chest X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), CT in conjunction with positron emission tomography (PET). Age, sex, sub site, clinical stage, pathological response to NACT, adjuvant therapies, date at which disease recurrence was detected, and oncologic results at the most recent follow-up examination were all noted as patient characteristics and clinical features.

Before starting therapy, head and neck surgeon, radiation oncologist, and medical oncologist evaluated the patient and made treatment decision. The Union for International Cancer Control (UICC) TNM Classification was used for the clinical tumour staging (eighth edition). In borderline resectable cases with locally advanced disease where an appropriate surgical margin is not attainable due to tumour dissemination up to the zygoma and/or soft tissue swelling up to the zygoma, significant involvement of the infratemporal fossa and substantial involvement of soft tissues up to the hyoid, NACT was primarily taken into consideration.

NACT recipients were under age of 75 years, having an ECOG performance status of 0 or 1. NACT standard treatment plan consisted of two or three cycles of the drugs (5-FU + Cisplatin + Docetaxel or Paclitaxel + Carboplatin). Minimum three weeks following NACT, the final surgery was done. The surgical resection was planed taking into account the tumour extension following NACT.

In addition to primary tumour excision, neck dissection and/or reconstructive surgery was carried out as a standard procedure. Depending on the final histopathology report, radiation therapy (60 Gy) was chosen as postoperative adjuvant therapy. If there was a positive/close surgical margin (i.e., the tumour was located within 5 millimetres of the surgical margin) or extracapsular extension, postoperative adjuvant radiation therapy (60-66 Gy) with platinum infusion was typically administered within 6 weeks of the operation.

Pathological Response Evaluation:

All samples were evaluated.With the use of NACT, a number of histopathological changes were observed in both the tumour itself and the metastatic lymph node. Necrosis, fibrosis/collagenization, blood vessel hyalinization, microcalcification and neovascularization have all been seen in the stroma, enhanced host inflammatory

response, which predominantly consisted of big, lymphocytic, and histiocytic cells with viable or non viable tumour cells in background was assessed.

Response Classification:

The surgical specimens were thoroughly examined by pathologists at Kailash Cancer Center, who classified the pathological effects of NACT as 3 Categories

1. Complete response: No viable tumour cells with changes mentioned above due to NACT
2. Partial response: Viable tumour cells with changes due to NACT >20%
3. No response: Viable tumour cells with changes due to NACT <20%

Margin assessment:

Three dimensional margins also assessed in all specimens and margins classified as free, close and positive margin.

Free margin was the distance from the invasive tumor front to the resected margin that was 5 mm or more.

Close margin was the distance from the invasive tumor front to the resected margin that is between 1 to 5 mm.

Positive margin is carcinoma in situ or as invasive carcinoma at the margin of resection or margin is 1mm.

Results:

Statistical Analysis:

Kaplan Meier Statistical analysis was used to determine the survival and clinical outcome of patients. IBM SPSS statistics version 23.0 was used for analysis.

Patient characteristics

There were 87 patients, with an age range from 26 to 73 years, 64 men and 23 women. Out of 87 patients, 58 (66.7%) had tumour involving the buccoalveolar complex, 27 (31%) tongue and 2 (2.3%) MOU (Figure1). 33 patients (37.9%) had N0 nodal status, 28 (32.2%) had N3b and 8 (9.2%) with each N1, N2a, N2b nodal status. 6 patients (6.9%) had T0 and 38 patients (43.7%) had T4 primary lesions. Seven (8%) patients and fourteen (16.1%) patients, respectively, had close and positive margins (Table1).

Treatment Characteristic:

All patients had ablative surgery minimum three weeks after receiving NACT (median= 35 days), 76 patients received 5-FU + Cisplatin + Docetaxel out of which 67 individuals received 2 cycles and 9 received 3 cycle, while 11 patients received paclitaxel + carboplatin, 9 individuals received 2 cycle and only 2 received 3 cycle.

Based on the final HPR, postoperative radiotherapy/chemoradiotherapy (RT/CRT) was planned. Of the total number of 87 patients, 49 patients (56.3%) received CRT as adjuvant therapy, 11 received RT, and 2 did not require any adjuvant. 25 individuals out of 87 defaulted for adjuvant therapy (Table1).

Pathological response to NACT

Pathological response post NACT and surgery was assessed. The majority, 54 of the 87 cases (62.1%), showed at least some degree of pathological response, while 33 cases (37.9%) had no response. In 46 (52.9%) of the 87 patients, partial response was seen, and in 8 (9.2%), complete response was seen, comprising of 2 MOU cases that underwent only neck dissection (Figure2). Seven patients (8%) and fourteen (16.1%) patients, respectively had close and positive margins rest 64 cases (73.6%) were having free margins, 2 patients were excluded as margin was not applicable.47(56%) and 32(36.8%) had PNI and LVI present respectively.

Prognostic impact of pathological response to NACT

Out of total 87 cases which were included in study 25 lost follow up so prognostic response was noted in 62 patients, the minimum follow-up period was considered 18 months, after a median follow-up of 42 months, the overall survival (OS) for 62 patients was 43.5%. There was no statistically significant difference in OS (P= 0.058) amongst three groups were noticed.

Though, the OS was 83.3% in the complete response group, 6 out of 6 patients survived till duration of 6 to 12 months, 5 patients survived till duration of 24 to 36 months, 4 patients for duration of 36 to 48 months and only 2 for more than 48 months.

OS was 43.8% in the partial response group, out of 32 patients, 30 patients survived for duration of less than 6 months, 19 patients survived for duration of 6 to 12 months, 10 patients survived till duration of 24 to 36 months, 7 patients survived for duration of 36 months to 48 months and only 2 for more than 48 months.

OS was 33.3% in the no response group, 18 out of 24 patients survived for duration of less than 6 months, 10 patients survived for duration of 6 to 12 months, 9 patients survived for duration of 12 to 24 months, 7 survived for duration of 24 to 36 months, 4 patients survived for duration of 36 to 48 months and only 2 for more than 48 months. The OS in the NACT groups with complete and partial responses was considerably higher than that in the no response (Figure5).

For all 62 patients, the DFS was 35.5%. The DFS was 50% in the complete response, 6 out of 6 patients survived disease free till duration of 6 to 12 months, 5 patients survived disease free till duration of 24 to 36 months and only 1 for more than 48 months.

DFS was 37.5% in the partial response, 28 out of 32 patients remain disease free for duration of less than 6 months, 17 patients survived disease free for period of 6 to 12 months, 15 patients till the duration of 12 to 24 months, 10 patients for duration of 24 to 36 months, 5 patients for duration of 36 to 48 months and only 1 for more than 48 months.

DFS was 29.2% in the no response group, 17 out of 24 patients survived disease free for duration of less than 6 months, 9 patients till the duration of 12 to 24 months, 7 patients for duration of 24 to 36 months, 3 patients for duration of 36 to 48 months and only 1 for more than 48 months. DFS is better in complete response and partial response NACT groups than the no response group. Although there was no statistically significant difference in the DFS between the three groups (P=0.174) (Figure5).

Out of total 62 cases, 27 patients develop recurrence and distant metastasis, 19 cases found to develop recurrence at locoregional site while 8 individuals develop distant metastasis. Out of 19 locoregional recurrences, 9 were in no response group, 8 in partial response and 2 in complete response group and 15 were having free margin, 3 having positive margin and only 1 having close margin. Out of 8 distant metastasis, 6 in partial response group and 2 in no response group while no distant metastasis noticed in complete response group and of these 8 patients, 4 had lung metastasis, 2 with liver metastasis, 1 with bone metastasis and 1 developed skin nodule over occipital region.

Disease free duration vs recurrence or distant metastasis was analyzed, in case of positive / close margin recurrence / distant metastasis found to develop early compared to free margin. Though no statistically significant difference was found as sample size was small (p=0.322) (Figure7). Disease free survival (DFS) was found to be better in cases with free margin as compared with positive / close margin (p=0.74) (Figure8). 22 patients died of disease and 13 died of other reason.

Discussion

The purpose of this study was to assess how NACT affected the prognosis in pathologically advance OSCC undergoing surgery. Theoretically, NACT administration prior to surgery or radiation therapy could reduce the incidence of distant metastasis and control locoregional disease. An improved prognosis may result from these advantages. NACT complete responder provided good prognostic value despite DFS and OS in the entire group being statistically similar. In head and neck cancer, the clinical and pathologic response to NACT is a significant prognostic factor [5, 7]. The outcomes were same with other research on NACT for OSCC [2, 8, 10].

Licitra et al. reported the efficacy of NACT followed by routine surgery for avoiding both extensive surgery, such as mandibulectomy, and postoperative radiation therapy, without a significant difference in OS in patients with advanced OSCC. This was done in a randomised, multicenter experiment [2]. NACT followed by surgery in resectable advanced head and neck cancer was shown to be beneficial by Cho et al [12]. In their series, individuals who received NACT together with surgery outlived those who received NACT along with radiation.

We were unable to assess whether less aggressive treatment and skipping postoperative adjuvant therapy is appropriate based on the pathologic response to NACT because the current investigation was retrospective. However, patients who completely respond to NACT display superior DFS versus those who do not.

A retrospective study of 123 patients with technically unresectable locally advanced oral cavity malignancies was published by Patil et al. In these instances, disease was defined as unresectable, extending up to the zygoma and/or soft tissue swelling up to the zygoma, significant involvement of the infratemporal fossa and substantial involvement of soft tissues up to the hyoid cartilage. The patients resectibility was evaluated after receiving NACT with TPF or TP. The three drug and two drug regimens had response rates of 32.00% and 27.37%, respectively. They showed that NACT can successfully downstage tumor, permitting aggressive surgery with a survival time of 2 years comparable to primary surgery.

In TAX 323 and 324 4 and 3 cycles of TPF was used while in the PARADIGM and DeCIDE study,3 and 2 cycles of TPF were used respectively, no advantage seen by giving more than 4 cycle in any study, so in our study 2 or 3 cycles were given according to tumor response.

In our study pathological response assessment was done on the basis of institutional criteria and cases divided amongst complete response, partial response and no response groups. Out of total 87 cases, 58 cases were of buccoaveolar complex 40.2% (35) shows partial pathological response. While in case of complete response out of total 8 cases, 50 %(4) were of tongue. Cases with complete response or partial response to NACT showed a good prognostic benefit in terms of OS and DFS than no response group. Cases with free margin have prolong disease free duration both in terms of locoregional or ditstant metastasis when compared with positive or close margin. Though statistical values were not significant as the sample size was small which is the only drawback of study.

Till date there is no standard clinical guideline for determining the pathological response and its impact on prognosis. More studies should be conducted to make standard guidelines for the pathological tumor response, so that its impact on survival can be assessed in multicentric studies.

Conclusion

In our study one third of patients defaulted for adjuvant treatment and follow up. In complete response group tongue lesion shows better response than buccoavleolar complex lesion. Complete response group shows better DFS and OS than no response group. The pathological response to NACT may be a significant prognostic indication for advanced OSCC even if NACT had a limited impact on the disease progression in OSCC. In locally advanced OSCC, preoperative NACT as a gateway appears to provide encouraging outcomes. These findings need to be confirmed, and large, multicentric studies should be conducted in order to identify the precise biomarkers that can be used to predict tumor response.

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Table 1. Patient Characteristic

Total n =87			Complete Response	Partial Response	No Response
N =87			Complete Response	Partial Response	No Response
Sex					
	Male	64 (73.6%)	6 (6.9 %)	34 (39.1%)	24 (27.6%)
	Female	23 (26.4%)	2 (2.3%)	12 (13.8%)	9 (10.3%)
SubSite					
	Buccoalveolar Complex	58 (66.7%)	2 (2.3%)	35 (40.2%)	21 (24.1%)
	Tongue	27 (31%)	4 (4.6%)	11 (12.6%)	12 (13.8%)
	MUO	2 (2.3%)	2 (2.3%)	0	0
Pathological T Stage					
	Tx	2 (2.3%)	2 (2.3%)	0	0
	T0	6 (6.9%)	6 (6.9%)	0	0
	T1	7 (8%)	0	7 (8%)	0
	T2	9 (10.3%)	0	6 (6.9%)	3 (3.4%)
	T3	25 (28.7%)	0	13 (14.9%)	12 (13.8%)
	T4	38 (43.7%)	0	20 (23%)	18 (20.7%)
Pathological N Stage					
	Nx	2 (2.3%)	0	1 (1.1%)	1 (1.1%)
	N0	33 (37.9%)	7 (8%)	15 (17.2%)	11 (12.6%)
	N1	8 (9.2%)	0	8 (9.2%)	0
	N2				
	a	8 (9.2%)	0	6 (6.9%)	2 (2.3%)
	b	8 (9.2%)	0	4 (4.6%)	4 (4.6%)
	c	0	0	0	0
	N3b	28 (32.2%)	1(1.1%)	12 (17.2%)	15 (13.8%)
Margin					
	Positive	14 (16.1%)	0	10 (11.5%)	4 (4.6%)
	Close	7 (8%)	0	1 (1.1%)	6 (6.9%)
	Free	64 (73.6%)	6 (6.9%)	35 (40.2%)	23 (26.4%)
	Not Applicable	2 (2.3%)	2 (2.3%)	0	0
PNI	Present	47 (54%)	0	24 (27.6%)	23 (26.4%)
	Absent	38 (43.7%)	6 (6.9%)	22 (25.3%)	10 (11.5%)
	Not Applicable	2 (2.3%)	2 (2.3%)	0	0
LVI	Present	32 (36.8%)	0	17 (19.5%)	15 (17.2%)
	Absent	53 (60.9%)	6 (6.9%)	29 (33.3%)	18 (20.7%)
	Not Applicable	2 (2.3%)	2 (2.3%)	0	0
NACT					

	5-FU + Cisplatin + Docetaxel	76	8	38	30
	Paclitaxel + Carboplatin	11	0	8	3
Number of Cycle					
5-FU + Cisplatin + Docetaxel	2	67	8	34	25
	3	9	0	4	5
Paclitaxel + Carboplatin	2	9	0	7	2
	3	2	0	1	1
Post OP Adj					
	RT	11	3	5	3
	CTRT	49	4	28	17

Figure 1 Subsite Distribution.

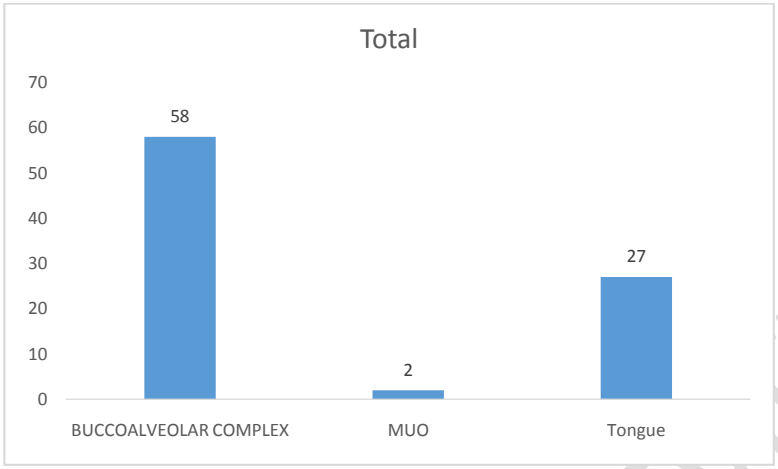

Figure 2 Response wise distribution

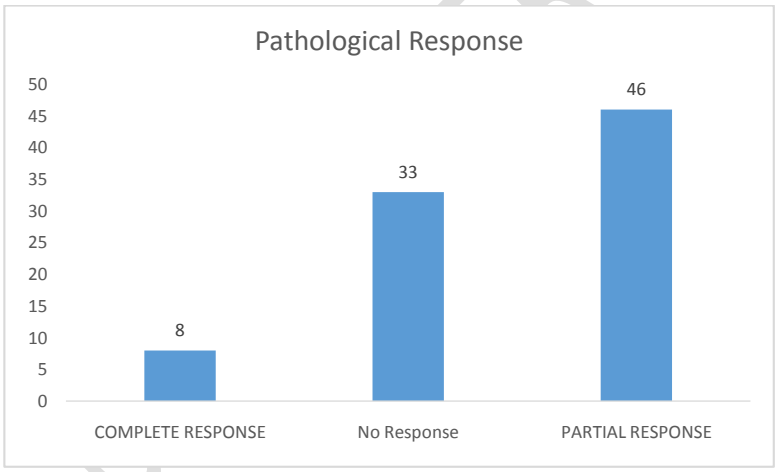

Figure 3. Overall Survival

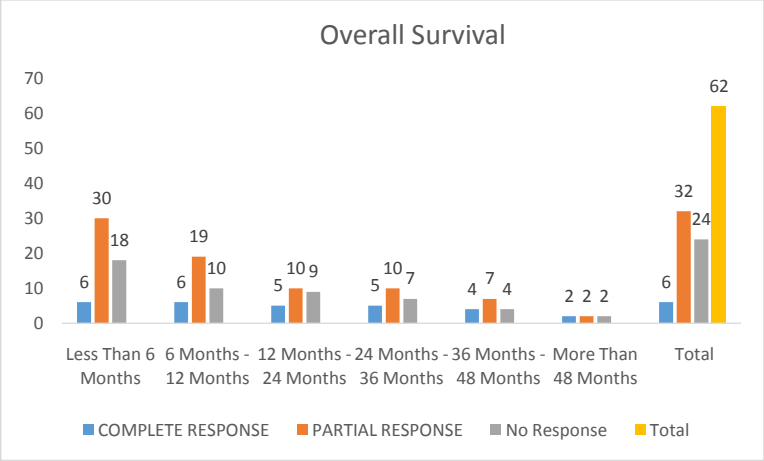

Table 2 Overall Survival

	Overall Survival						
	N=62	Less than 6 Months	6 Months to 12 Months	12 Months to 24 Months	24 Months to 36 Months	36 Months to 48 Months	More than 48 Months
Compltete Response	6	6	6	5	5	4	2
Partial Response	32	30	19	10	10	7	2
No Response	24	18	10	9	7	4	2

Figure 4. Overall Survival

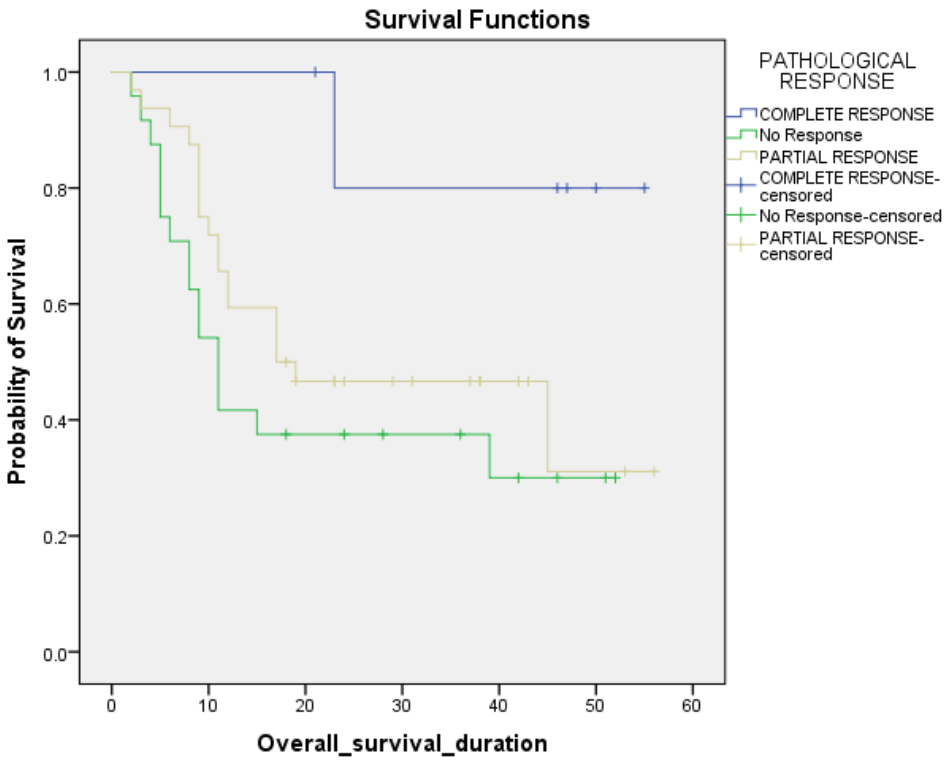

Fig 5. Disease Free Survival

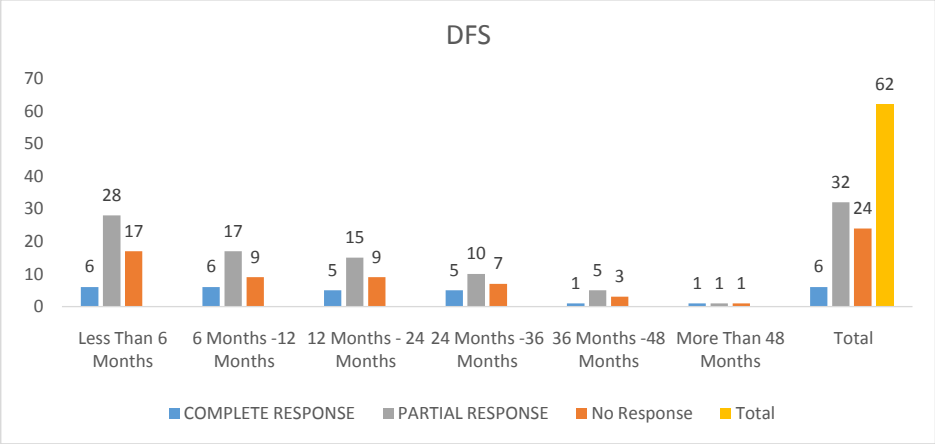

Table 3 Disease Free Survival

	Disease Free Survival						
Pathological Response	N=62	Less than 6 Months	6 Months to 12 Months	12 Months to 24 Months	24 Months to 36 Months	36 Months to 48 Months	More than 48 Months
Compltete Response	6	6	6	5	5	1	1
Partial Response	32	28	17	15	10	5	1
No Response	24	17	9	9	7	3	1

Figure 6. Disease Free Survival

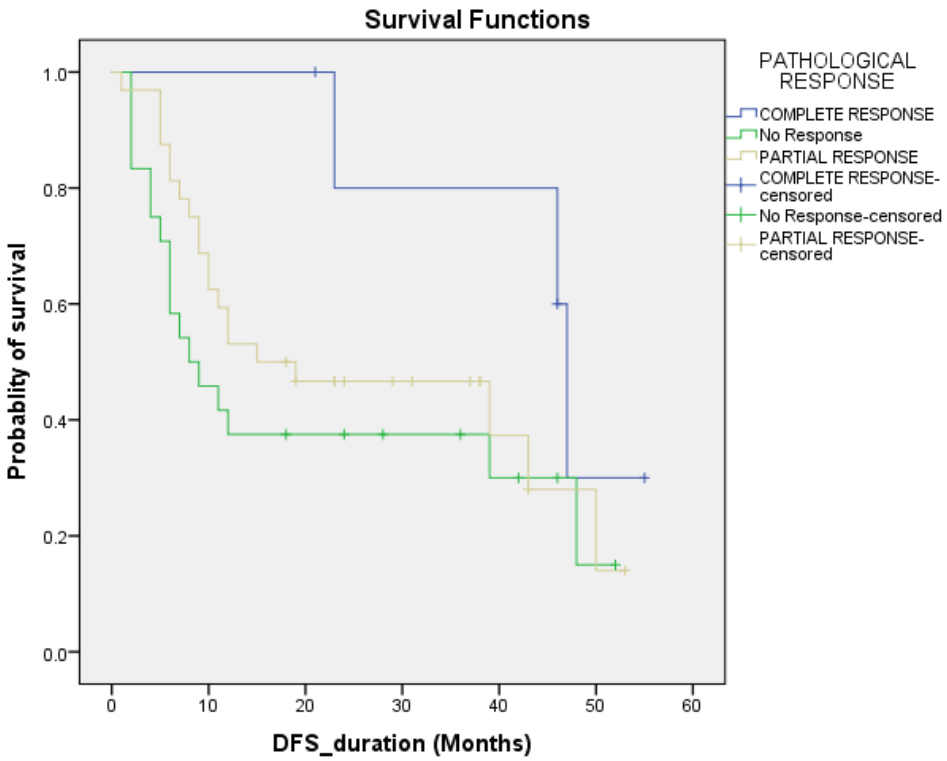

Table 4 Recurrence / Distant Metastasis relation with Margin & Duration

	N=27	Less than 6 Months	6 Months to 12 Months	12 Months to 24 Months	24 Months to 36 Months	36 Months to 48 Months	More than 48 Months
Positive Margin	4	2	2	NA	NA	NA	NA
Close Margin	3	NA	2	1	NA	NA	NA
Free Margin	20	7	7	NA	NA	5	1
Total	27	9	11	1	NA	5	1

Recurrence / Distant Metastasis relation with Margin and Response							
	N= 27	Complete Response		Partial Response		No Response	
		Locoregional Recurrence	Distant Mets	Locoregional Recurrence	Distant Mets	Locoregional Recurrence	Distant Mets
Positive Margin	4	NA	NA	2	1	1	NA
Close Margin	3	NA	NA	NA	1	1	1
Free Margin	20	2	NA	6	4	7	1
Total	27	2	NA	8	6	9	2

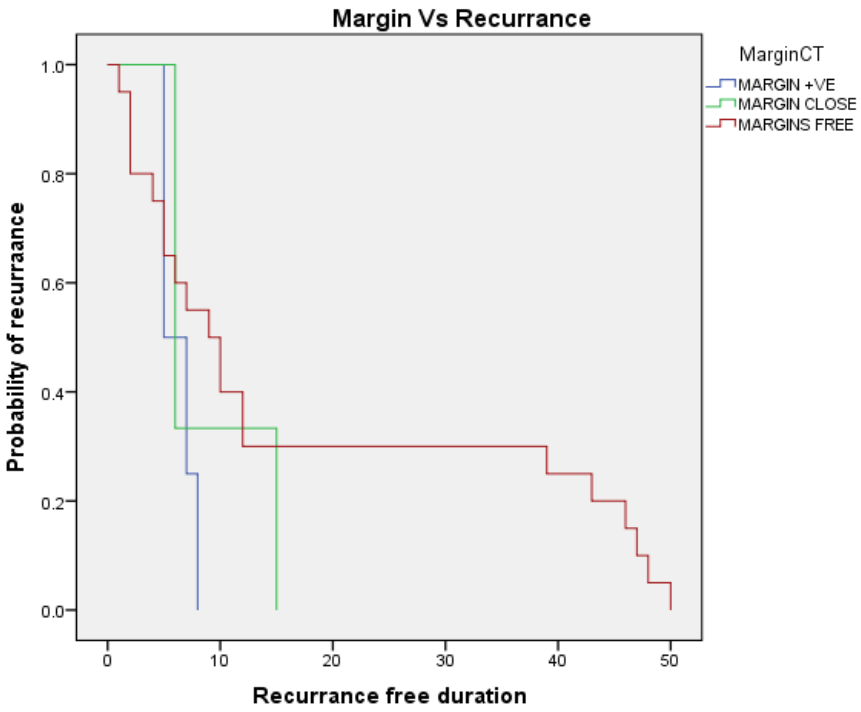

Figure 7. Margin Vs Recurrence

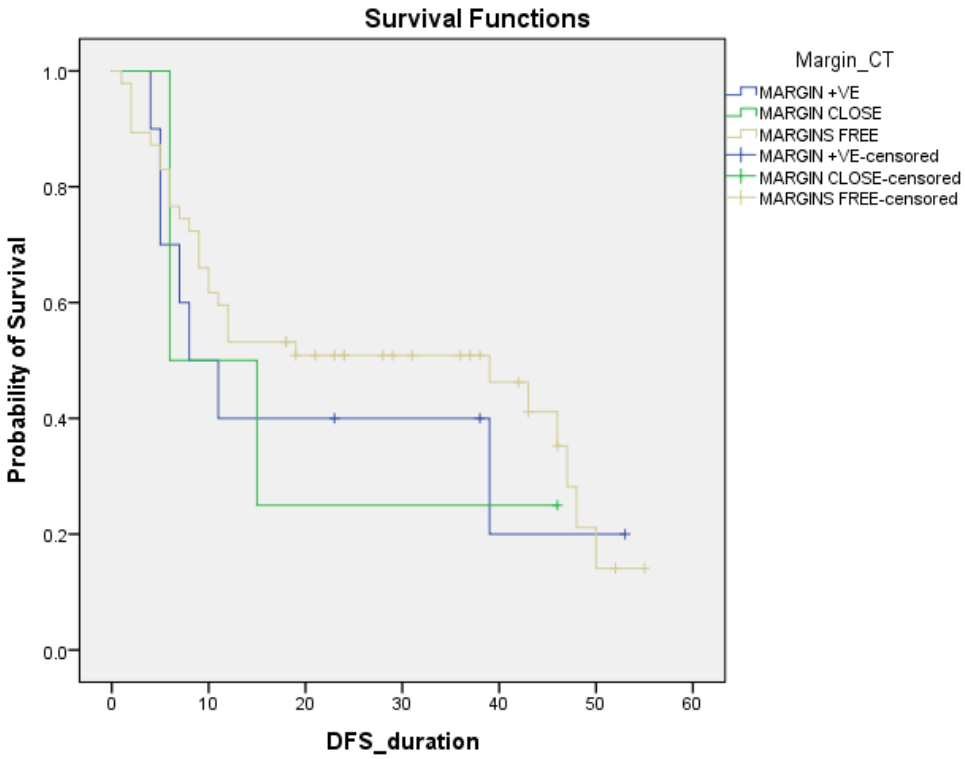

Figure 8. Margin Vs Disease free Survival