Original Research Article

Induction Chemotherapy as a predictor for definitive treatment in bulky Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A schedule more suited to sub Himalayan region

ABSTRACT

Purpose: Use of induction chemotherapy (IC) as a predictor for definitive treatment in bulky locally advanced head and neck cancer (LAHNSCC) patients, who are not feasible for any upfront radical treatment in sub-Himalayan population.

Materials And Methods: 33 patients (stage IVA and IVB, T4, N3) LAHNSCC were treated with induction chemotherapy (TP) from April 2013 to August 2015. All patients were considered inoperable or not feasible for upfront radical treatment and Eastern Cooperative Oncology Group (ECOG) Performance status was ≤ 2.

All patients were reviewed at multidisciplinary tumor+ board and considered for initial 3 cycles of induction chemotherapy in view of bulky stage IV LAHNSCC. Subsequent Radical (CTRT or Sx → CTRT) or palliative treatment was decided by tumor board after response assessment of NACT. The Statistical Package for the Social Sciences software (SPSS version 16.0) was used for analysis. The response rates, toxicity (accordance with CTCAE *vs*. 4.02), completion rate of radical treatment post NACT and overall survival are reported.

Results: Median follow up was 22 months (18-26 months).After 3 cycles of IC, 20 patients (60.66%) underwent radical treatment and remaining 13 patients (39.33%) were treated with palliative treatment. Overall grade 2-3 toxicity was seen in 12 patients. No toxicity related mortality was noted. The completion rate of radical treatment post IC was 93.5%. The median OS was 18 month ((95% CI 9.00 to 31.00). Total 16 Patients are alive, in which 11 are disease free. Twelve patients are died and 5 patients are lost to follow up

Conclusion: Our present experience suggests that neoadjuvant chemotherapy with doublet regime is reasonably well tolerated and feasible in a limited resources settings of patients with locally advanced disease who are not fit for upfront radical treatment.

Keywords *: Locally advanced head and neck cancer, neoadjuvant chemotherapy, Radiotherapy, predictor for definitive treatment in head and neck cancer*

INTRODUCTON

Head and neck cancer is the most common cancer in India (1-3). There are high incidence of HNSCC in developing countries like India. Use of tobacco is considered as a risk factor for the development of HNSCC. Advanced loco-regional disease, defined as either non-metastatic Stage III or Stage IV, is the most frequent clinical situation appearing in 60% of the diagnosed patients. For the loco-regional disease, an acceptable option is a local treatment based on surgery and/or radiotherapy (RT). On the other hand, in the treatment of inoperable, loco-regionally advanced HNSCC the principal treatment in most institutions is combined-modality treatment with chemo-radiotherapy (CRT). If patient is

medically fit. This last approach has become the standard treatment for most patients. A majority of patients with squamous cell carcinomas of the head and neck (SCCHN) have stage III-IV disease at diagnosis in India. The 5-year survival rates of multimodal chemo-radiotherapy are below 20%, with a median survival of 12 months or less (1-3).

Although role of induction chemotherapy is still investigational, sequential treatment with induction chemotherapy followed by radical treatment for SCCHN has been shown to decrease the risk of distant metastases as a first site of tumor recurrence and may lead to favourable functional outcomes. (3-4)

Induction chemotherapy with TPF has gained popularity because of the edge they have in terms of disease response and possible survival benefit over other combinations that were in use earlier (5). However, the debate on survival benefit continues. Recent studies reveal

No significant benefit in OS with sequential chemoradiation following induction chemotherapy as opposed to concurrent chemoradiation alone for locally advanced head and neck cancer (5, 6, 7).

Although TPF is widely in use as the combination of choice for neoadjuvant chemotherapy in head and neck cancers, the incidence of toxicities remains considerable, and the supportive treatment required is often resource intensive.

There are a lot of challenges in sub-Himalayan population, who are planned for neoadjuvant chemotherapy. Most common cited reason is financial difficulties. Despite of extremely subsidised treatment.

Another common reason is that patients preferred traditional healers. Use of traditional medicines are very common.

Last but most important is logistic reason. This is due to many patients travel from hilly terrain, which often gets subjected to natural difficulties such as landslides during autumns, and snow –blockade of roads during winters. Indeed, being the only cancer centre in the Garhwal region, patients travel for long distances, across difficult terrain for treatment.

Consequently, the impact of treatment toxicity is considerable; it imposes a financial burden on the patient's family and the healthcare system in general. The treatment interruptions that occur because of the toxicity also have a bearing on disease outcomes; the radiobiology of most head and neck tumours makes the issue of treatment gaps especially important in relation to tumour outcomes.

We treated patients with locally advanced nodal bulky disease with induction chemotherapy consisting of 3 weekly paclitaxel and cisplatin followed by "risk-based" definitive treatment consisting of concomitant chemo radiotherapy, or surgical resection based on the site and stage of disease at diagnosis followed by chemoradiotherapy/radiotherapy. Our hypothesis when we designed this study was that induction PC followed by risk-based local therapy would achieve long term locoregional and distant disease control with acceptable toxicity.

To our knowledge, there has been no specific study on patients who present with locally advanced squamous cell carcinoma of the head and neck (SCCHN), which represents between 1.5% and 16.8% of newly diagnosed cancer patients. However, it is noteworthy that in patients receiving treatment for the first time, the response rates of SCCHN to induction chemotherapy ranges from 68% to 72%, among the highest rates for solid tumors.5,6

We believe that there might be a subset of Stage IV bulky LAHNSCC patients. If we use induction chemotherapy, it helps in shrinking the tumour with acceptable toxicities and lead to definitive treatment with radical intent, either surgery and/or chemo-radiotherapy and non-responder patient requires only palliative treatment. At our centre, we are following this approach.

METHODS:

The treatment plan of patients presenting with head and neck cancers is decided in a multidisciplinary tumor board meeting at our centre. The patients with bulky locally advanced squamous cell head and neck cancers stage IV with ECOG performance status ≤2, who were technically unresectable or not feasible for radical treatment, were considered suitable for induction chemotherapy. The induction chemotherapy protocol used in our center is a double or triple regimen consisting of a taxane and a platinum agents with or without 5-fluorouracil.

We retrospectively evaluated, Thirty three patients (stage IVA and IVB) of LAHNSCC, who were treated with double regimen induction chemotherapy from April 2013 to July 2015.

Out of 33, 7 patients were IVA (T4a and N2c) and rest 26 were IVB (N3 >6 cm) respectively. In all patients ECOG Performance status were ≤ 2

Patients, who had uncontrolled comorbidities like hypertension, diabetes mellitus, cardiac dysfunction or any other uncontrolled disease excluded from study.

All patients were reviewed at multidisciplinary tumor board and considered for induction chemotherapy in view of bulky stage IV LAHNSCC. Subsequent Radical or palliative treatment was decided by tumor board after response assessment of NACT.

After histopathological diagnosis, pre-treatment investigations included complete blood count, renal biochemistry, chest radiography, dental assessment and CT scan of head and neck for tumor assessment.

Induction Chemotherapy

All patients were treated with 3 weekly IC (Taxane and Cisplatin) at a dose of Inj paclitaxel 175mg/m2 and inj. Cisplatin 75 mg/m2. 31 patient's received three cycles of induction chemotherapy. Remaining 2 patients had only two cycles of chemotherapy because of poor response of chemotherapy.

Toxicity related to chemotherapy was assessed at each visit prior to chemotherapy. Assessment of toxicities were recorded according to CTCAE version 4. Delay in planned treatment was noted.

After completing three cycles of induction chemotherapy, tumor response was assessed by RECIST Criteria

Patient who had response (CR+PR) underwent Radical treatment (CTRT or Sx-CTRT) and non-responders were treated with palliative treatment.

Surgery

Surgery included wide local excision along with appropriate neck dissection and reconstruction. All patients underwent preoperative speech and swallowing assessments as well as counselling for nutrition.

Sequential chemoradiation

A total of 90% patients received conventional and 3D-CRT technique. A dose of 66Gy in 33 fractions @ 2Gy per fraction over six and one half weeks by 6 MV was prescribed.

All patients received weekly inj cisplatin 30mg per m2. Weekly complete Blood count and serum creatinine were monitored. All patients were examined every week during the course of chemo-radiation for toxicity. Radiation toxicity was assessed according to RTOG acute toxicity criteria and recorded every week.

After the completion of therapy, the patients were re-assessed clinically and radiologically in the multidisciplinary clinic. Based on the performance status, nutritional status, response to treatment and the status of comorbidities, further treatment could be surgery, radical radiation with or without chemotherapy, palliative chemotherapy or best supportive care alone. Patients, who had >30% response underwent radical treatment that could be surgery or chemoradiotherapy and < 30% responded patients had palliative treatment. The Statistical Package for the Social Sciences software (SPSS version 16.0) was used for analysis. The demographic details, status of disease, details of the chemotherapy including the toxicity according to the CTCAE version 4.02 (common terminology criteria of adverse events), response rate to NACT (RECIST version 1.1), completion

rate (Cp) of radical intent treatment post induction chemotherapy (IC), progression free survival (PFS) and overall survival (OS) are reported

Dietitian prior to radiotherapy. Prophylactic feeding tubes were not placed unless nutritional compromise and/or dysphagia were identified in baseline assessments. Statistical methods Descriptive statistics were calculated to describe the sample characteristics, toxicity, and functional outcomes. Survival distributions were estimated using the Kaplan-Meier method. Statistical differences between paired data were analyzed using the nonparametric sign-rank test. Statistical significance was considered α-level 0.05.

RESULTS:

Sample characteristics thirty three patients with previously untreated stage IV SCCHN were enrolled. Median follow up of patients was 22 months (18-26 months) and the median age was 52(30-74) years; 30 patients were male and rest 3 were females. Site wise distribution was as follows: oral cavity- 14 (42.43%), oropharyngeal-7 (21.21%), laryngopharynx-8(24.24%) and unknown primary with neck secondary UNP-4 (12.12%) respectively. Table-1 depicts all patient's characteristics. The response was assessed in 33 patients after completion of 3 cycles of induction chemotherapy. 20 patients (60.60%) were having > 30% response, following which they underwent radical treatment and remaining 13 (39.40%) were treated with palliative treatment.

On site wise subgroup analysis of palliative treated (<30% response) and radically (>30% response) is depicted in figure-1 and Table-2.

Out of 14 patients of oral cavity, resectability and suitability for surgery could be achieved in 7 patients. However, only 3 patients of buccal mucosa finally underwent surgical resection followed by adjuvant chemoradiotherapy, and rest 4 refused for surgery and treated with radical chemo radiation.

The remaining patients in Arm A were treated with Palliative radiotherapy.

Thus, the calculated completion rate (Cp) of radical intent treatment was 93.5% as 19 of 20 patients completed radical intent treatment.

Toxicity:

At the end of treatment maximum 12 patients had grade 2 mucositis, 4 patients had grade 3 mucositis and 2 patients developed grade 2 haematological toxicities in radical treatment group. No toxicity related mortality was seen.

In Arm A, Thirteen patients underwent palliative radiation. Median PFS in palliative group was 5 months (95% CI 2.6-9.4 months)

In Arm B, twenty patients were treated by definitive treatment after IC. Table 3 depicts status of patients in arm A at the time of analysis.

The median OS is 18 month ((95% CI 9.00 to 31.00) [Figure-2]. There is a significant (p=.001) difference in survival in both arms. (Figure-3)

Total 16 Patients are alive, in which 11 are disease free, 12 patients are died and 5 patients are lost to follow up. (Table-4)

As the number of patients is small, no univariate or multivariate analysis was possible

DISCUSSION

Locally advanced bulky head and neck squamous cell cancer patients with ECOG performance status of 2 or less, who are unresectable bulky and considered unsuitable for any radical treatment and are often treated with palliative radiation alone. (8-10) such an approach has been reported previously from India and is associated with unsatisfactory survival outcomes. Mohanti et al., treated 578 patients with a uniform palliative schedule of 20 Gy/5# over 5 days.(8) The median survival was only 200 days (6.++ months). Though all sub-sites in head and neck

cancers were included in the study, oropharyngeal cancers were predominant (233 patients, 46%). Oropharyngeal tumours are frequently associated with HPV and such tumours normally have a favourable prognosis. (16,17) All the patients had stage IV disease. However, only 30% had stage IVB while 43.16% had non T4 disease (T1-T3).The early results of this phase II trial are favourable with respect to disease control, but also demonstrate encouraging long-term functional outcomes. [11, 12]

Ghosal et al., reported the results of QUAD shot therapy from another centre in north India.Fifteen patients were treated with QUAD shot and had good symptom relief but with a median PFS of just12 weeks.(9,10)

Agarwal et al., published results of 110 patients treated with an alternative schedule of 40 Gy given in 16# over 3.1 weeks. Similar to the previous report, the most common subsite was the oropharynx (41%), 50% patient had a KPS (Karnosky performance status) equal to or above 70 and non T4 disease was present in 22% of patient. In this report, the median local progression free survival was around 1 year. The PFS (including local and distant progression) and OS were not reported. These series from major centers in India show that palliative radiation is often used for symptom relief when tumors are not considered curative. Interestingly, despite the majority of the tumors belonging to favourable subsites like the oropharynx, good performance status and stage IV A disease, palliative RT was preferred over radical treatment. Though no reasons are mentioned by the authors, it can be surmised that extensive disease and limited resources may have swayed the decision to use palliative treatment only. (11)

IC is used with the goal of reduction of tumor volume prior to definitive treatments. Other biological advantages include a potential efficacy against systemic micrometastases. However, prolongation of the overall treatment time has been a point against the widespread acceptance of IC as a routine standard of care. Even though survival benefit has not been noted, several

studies have demonstrated a benefit in terms of tumor volume reduction and as well as in the reduction of distant metastases. (12, 13)

While initial studies were mostly with the use of doublet-IC, recent studies have shown more favorable outcomes with the use of triplet regimens, by the addition of taxanes to the usual cisplatin and 5-fluorouracil.(14,15) Response rates with IC are reportedly as high as 80%, with about half of the responding patients demonstrating complete responses.(12,13)

This exploratory study demonstrates the effectiveness and tolerability of induction chemotherapy using TP for LAHNSCC compare to TPF. The response rate of 60% is comparable to the 68-80% response rate observed with TPF in randomized trials and in routine practice (5, 6,15).

Interestingly, TP was tolerable since we did not observe toxic death; but TAX 323 has reported 83% patients had grade 3 and 4 febrile neutropenia (6).

Despite the good response rates with IC, the prognosis of the nonresponding population can be regarded as poor. It is due to the rationale that nonresponse to IC often is an indicator of subsequent radioresistance. Reasons include potentially enhanced repair mechanisms against cytotoxic insults such as radiation and chemotherapy. Another reason could be possibly because of a high proportion of dormant cells in the tumour, which could compromise radiosensitivity and chemosensitivity, since cytotoxicity is maximum upon actively dividing cells. (12, 13, 18, 19)

We considered the response to induction chemotherapy to be an important prognostic factor which may determine the sequence and timing of further planned definitive therapy: patients with lesser response patients were treated with palliative treatment. Therefore, on the basis of the evaluation made after induction chemotherapy, we adopted a flexible protocol, based not only on the patient's compliance and general conditions, but mainly on their response to neoadjuvant

chemotherapy. A similar but less customized multimodality treatment has been followed by Kovacs et al. (20) in a large series of oral and oropharyngeal cancer patients

Our results show some noteworthy features. Despite nearly all the patients having a performance of 2 or less, the tolerance to induction chemotherapy was acceptable. All patients completed the scheduled induction chemotherapy though there was no serious toxicity and there was no toxicity related death in our study. We believe that improved tolerance and response to chemotherapy could reflect improved nutrition and further treatment. The response rate of 60.7% noted in our study compares favourably with other published literature. The response rate is especially surprising considering the large proportion of oral cavity tumors and adverse prognostic factors. In our study, the conversion rate to resectability was around 50% and similar number of patients received radical intent treatment post- induction therapy. The impact of multimodality treatment was seen in median OS being 18 months. These results are better than the previously reported series with palliative radiation as shown in Table 5.

Table 5: Table comparing PFS and OS of different palliative RT schedules with present series.

Author Number	**PFS**	**OS**
Mohanti (8)	NR	200/400 days*
Ghoshal (9)	3 months	NR
Das (10)	NR	7 months

Corry (21)	3.1 months	5.7 months
Porceddu (22)	3.9 months	6.1 months
Present series	5 months	18 months

*Overall OS not reported. Patients given 20 Gy/5# had 200 days at OS, responding patients treated with more 20Gy/5# had 400 days as OS.

Table 6. Cetuximab: clinical program in squamous cell carcinoma of the head and neck: efficacy data in chemo-naıve patients

Reference	Type of study	No. of patients	Treatment arms	RR (CR) (%)	Median survival (months)
Burtness (2002) (23)*	Phase III	60	Platinum+ Cetuximab	26	9.3
		63	Platinum+ placebo	10	8
Humblet (2004) (24)	Phase I/II	27	Cisplatin +5-FU + Cetuximab	33	10.6
		26	Carboplatin+5-FU + Cetuximab	38	8.5

*Updated by Forastiere during ASCO 2004 ,

**Only local PFS in the irradiated area reported. NR=Not reported

Limitations

One of the drawbacks of our study is, it being a retrospective study in nature and the number of patients is quite small.

Conclusion

Our present experience suggests that in the treatment of bulky locally advanced head and neck squamous cell carcinomas with equal and less than 2 performance status were adopted doublet regime induction chemotherapy suited for sub Himalayans region as part of a first-line multidisciplinary approach, can achieve a high response rate, which may have a prognostic significance. Neoadjuvant chemotherapy with doublet regime is reasonably well tolerated and feasible in a limited resources settings of patients with locally advanced disease who are not fit for upfront radical treatment. Rather than treating with a palliative intent with poor outcome, our approach resulted in radical treatment in 60% of patients and can potentially improve outcomes in such patients.

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Base Line Characteristic	Result		
AGE	Mean : 52.70 years	Range : 30 – 74 years	Median : 54 years
SEX	Male : 31	Female : 2	
PERFORMANCE STATUS	ECOG PS II : 30	ECOG PS III: 3	
HISTOLOGY*	WDSCC : 5	MDSCC : 22	PDSCC : 6
PRIMARY SITE (SUBSITE)	**Oral Cavity : 14** Buccal Mucosa : 5 Tongue : 6 RMT : 1 Hard Palate : 2 **Oropharynx : 7** Tonsil : 3 Base Tongue : 4 **Laryngohypopharynx : 8** Pyriform Fossa : 5 Supraglottis : 3 **CUPS : 4**		
STAGE	IV A : 17	IV B : 16	
Co morbidities	DM : 3		
Radiotherapy Technique	2D : 13	3DCRT : 19	IMRT : 1

Table1: Showing the baseline characteristics of the patient cohort N = 33

*WDSCC - Well differentiated squamous cell carcinoma

MDSCC- Moderately differentiated squamous cell carcinoma

PDSCCC - Poorly differentiated squamous cell carcinoma

Primary site	**Subsite**	**.> 30% Response**	**<30% Response**
Oral cavity (14)	Anterior Tongue	3	3
	Buccal Mucosa	3	2
	Hard Palate	1	1
	Retro Molar Trigone	0	1
Oropharynx(7)	Base of Tongue	3	1
	Ca Tonsil	2	1
Laryngo hypopharynx(8)	Larynx	2	1
	Pyriform fossa	4	1
CUPS(4)		2	2

Table -2 Subsite wise response

Arm B (n=20)		
Alive without disease	11	
Alive with disease	Local Recurrence	3
	Nodal Failure	2
	Distant Mets	1
Loss in follow up		2
Death	1	

Table-3 Status of Radical treated patients

Status	Number Of Patients (N=33)	Percent
Alive without disease	11	33.3
Alive with disease	5	15.2
Death	12	36.4
LOF	5	15.2
Total	33	100.0

Table-4 Overall Status at the time of analysis

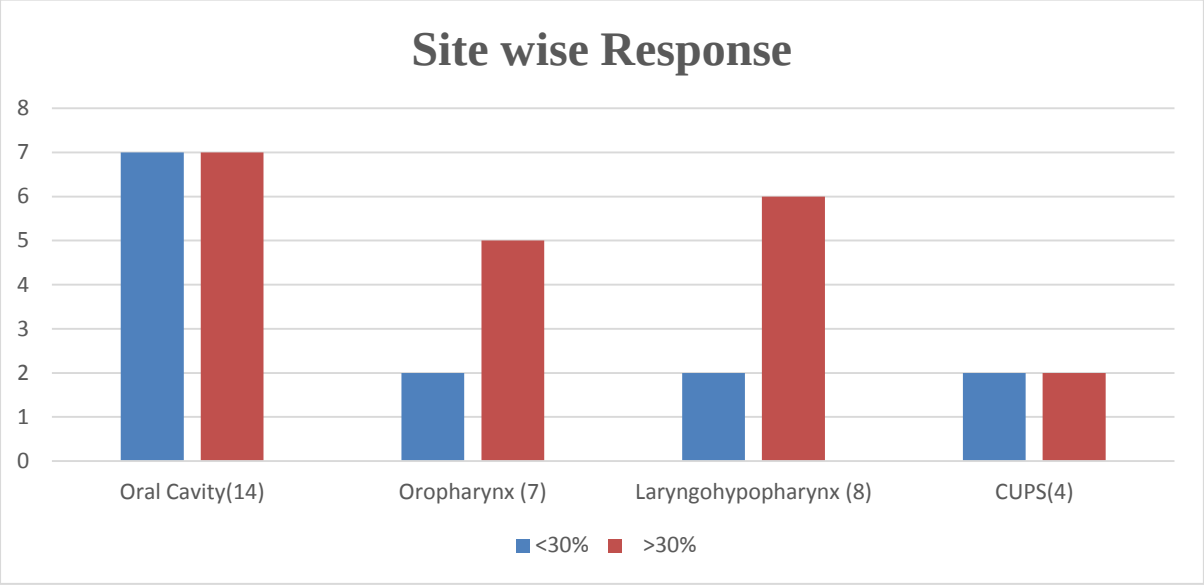
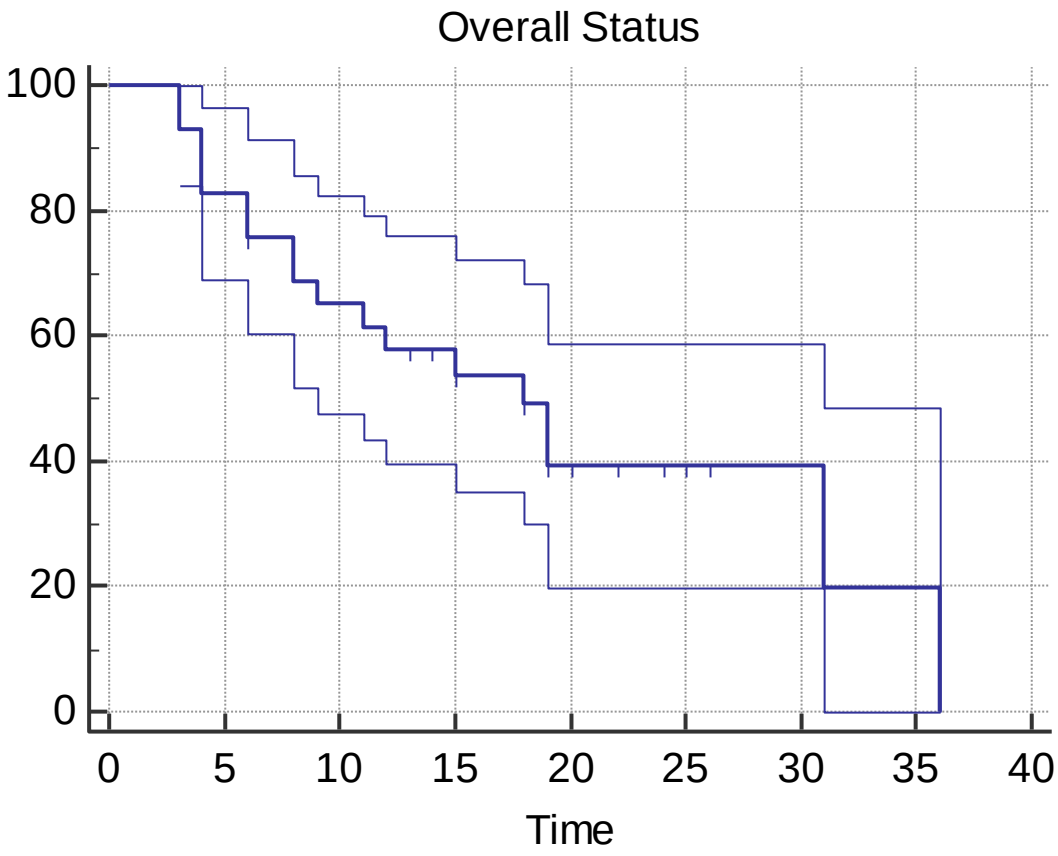


Figure-1



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376 **Figure-2**

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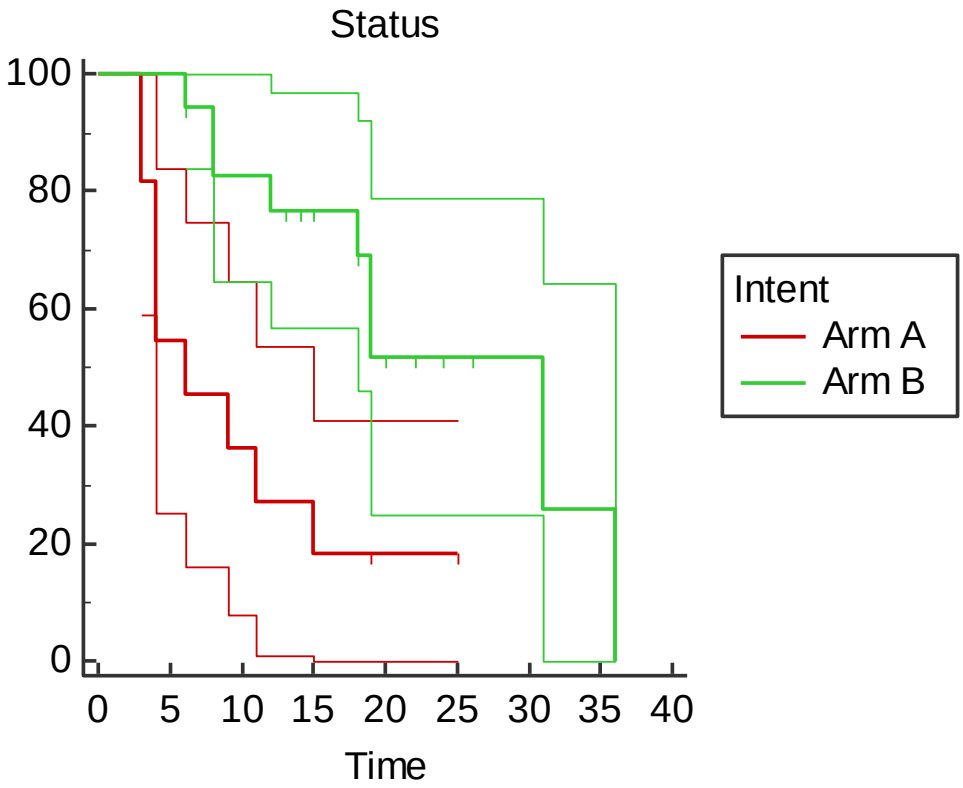
Status
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
Time
Intent
Arm A
Arm B

Figure-3