A PROSPECTIVE ANALYSIS OF THE UTILITY OF 18-FDG PET IN MERKEL CELL CARCINOMA OF THE SKIN:

A TRANS TASMAN RADIATION ONCOLOGY GROUP STUDY, TROG 09:03

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Key words: Merkel Cell Carcinoma, PET, Chemo-radiotherapy

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Article type : Radiation Oncology Original Article

Abstract

Introduction: TROG 09.03 prospectively studied the utility of Fluorine-18 Fluorodeoxyglucose (18-FDG) PET in the management of Merkel cell carcinoma of skin.

Methods: Following consent and registration, a pre-treatment FDG-PET/CT was performed. Sites of avid disease were confirmed by cytology where practicable. Following surgery, patients with AJCCv7 Stages IIA-IIIB disease were treated with chemo-radiotherapy and reassessed with a post treatment PET.

Results: Fifty-eight subjects (45 males and 13 females, median age 68 years) were enrolled between 2011 and 2015, 43 patients of whom went on to receive chemo-radiotherapy. An occult primary was present in 22(37.9%), T1 in 22(37.9%) and T2 disease in 14(24.1%). Nodal disease was present in 69% of cases. Fifty percent of subjects had gross residual disease at the primary site and/or nodal site at the time of registration. 18-FDG PET/CT had a sensitivity of 94.74% (95% CI 82-99.3%) and a specificity of 88.24% (95% CI 63.56-98.54). The positive predictive value was 94.74% (83.01-98.51) and the negative predictive value was 88.24% (95% CI 65.81-96.69). The pre-treatment PET influenced a treatment decision in 27.6% of cases. Upstaging occurred in 15(25.9%), with no down-staging. Other diseases were identified in 4(6.9%) patients. Univariate analysis failed to demonstrate that pre-treatment SUV levels or a negative post-treatment PET had any impact on overall survival. PET staged patients had 89% 3-year in-field loco-regional control and 76% 3-year overall survival.

Conclusions: Staging 18-FDG-PET significantly influenced treatment decisions in approximately one third of cases of MCC and should be considered in the routine pre-treatment work-up. Post-treatment PET was not found to be prognostic. Funding through the Medicare Benefits Schedule needs to be considered for high risk MCC.

1. Introduction

Merkel cell carcinoma (MCC) is considered to be a rare, aggressive form of skin cancer with a high propensity to spread to draining lymph nodes and to distant sites.[1] The 5-year survival of patients in Queensland was 41% and the most common cause of death was from distant metastases.[2, 3] Patients with MCC are often elderly and the potential toxicity from treatment is significant. The TROG 96.07 and 09.03 Phase II studies using radiation treatment and chemotherapy have helped shape a more standardised approach to this disease although it is fair to say there is still no universal consensus.[4] Given the aggressive biological nature of MCC and the patient demographic, careful pre-treatment staging is appropriate. It has been suggested that Fluorine-18 Fluorodeoxyglucose (FDG) Positron Emission Tomography/CT (PET) imaging prior to treatment may up-stage 25-33% of patients and alter the management in 14-43% of patients.[5, 6] A systematic review and meta-analysis of PET by Treglia et al demonstrated high sensitivity (90%) and specificity (98%) in a quantitative analysis of 6 studies involving 92 patients. [7]

The aim of this study was to identify the proportion of patients in which PET can influence the management of patients with MCC. A secondary aim was to assess the prognostic value of post-treatment PET.

2. Methods

2.1 Trial design

The Trans Tasman Radiation Oncology Group TROG 09.03 study (Clinical Trial Registration Number NCT01013779) was a Phase II design with a two-step registration process. To be eligible for the first step, the patient had to have biopsy proven MCC, be over the age of 18 years, have written informed consent, be able to undergo PET, be available for follow-up, use contraception if of child bearing age, be of Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and demonstrate adequate renal function and bone marrow reserve to tolerate the treatment protocol. Patients were ineligible if they were unable to comply with the protocol, if they had previous chemotherapy in the past 5 years or prior radiation treatment to the area of concern, previous cancer in the past 5 years other than non-melanomatous skin cancer, current pregnancy or lactation, immunosuppression, or any serious malignancy that precluded the safe delivery of treatment. Patients were only eligible for the second step (treatment registration) if they had American Joint Committee on Cancer Version 7 (AJCC v7) Stage IIA-IIB or recurrent MCC not previously treated with radiation treatment.,

The protocol was approved by each treating hospital ethics committees and written informed consent was obtained from all patients. Patients were registered on the study from December 2011 to October 2015.

2.2 Pre-Treatment Evaluation

Patients were staged with contrast CT of the primary site and draining lymph nodes, chest and abdomen according to the local institutional protocol. Full Blood Count, electrolytes and liver function tests were also performed. Baseline quality of life (QOL), tumour measurements, diagrams and photographs of the site were sent to the central trials office. Central pathology review was undertaken for all cases.

2.3 PET imaging protocol

The pre-treatment PET scan was performed within 6 weeks prior to commencement of radiation treatment. All clinically evident areas of increased FDG uptake were pathologically confirmed.
A strict PET imaging charter was provided in the study protocol to assist in the standardisation of the study conduct and patient preparation, supported by recording of acquisition data and parameters.
A post -treatment PET/CT was performed on patients in the treatment cohort 9 weeks post radiation treatment but no later than week 12.

2.4 Treatment

Surgery was often performed prior to referral to the oncology department. The extent of surgery was at the discretion of the local institution as it was impracticable to standardise surgical management in a heterogeneous disease population, across multiple institutions. Wide surgical clearance of the primary was not mandated nor was it a prerequisite to have nodal disease resected or positive margins re-excised.

With regard to the radiation treatment, the primary site was encompassed with a generous margin (3-5 cm) where possible. Bolus was applied around the primary site to ensure adequate dose to the surrounding dermal lymphatics. The draining lymph nodes were treated in continuity with the primary site, provided the nodes were within 20 cm of the primary. A dose of 50-54Gy to the ICRU reference point in 25-27 fractions, 5 fractions per week, was prescribed with the higher dose being to macroscopic disease and the lower dose to potential microscopically involved areas. Radiation treatment could be given either using electrons, 3-D conformal or Intensity Modulated Radiation Treatment (IMRT), Volumetric Modulated Arc Radiotherapy (VMAT) or tomotherapy.

Chemotherapy was prescribed only for patients who proceeded to the second step of registration. Carboplatin with an area under the curve (AUC) of two was administered weekly during the radiation treatment. This was followed by three cycles of adjuvant Carboplatin (AUC 4.5) and Etoposide (80mg/M^2 days 1-3) commencing 3 weeks after completing the radiation treatment.[8]

2.5 Quality Assurance

A detailed audit was performed on the first 20 patients to examine protocol compliance. This included a review of the clinical, chemotherapy and radiation details and an independent review panel outside of the treatment institution reviewed the pre-treatment investigations, GFR calculations and protocol violations for chemotherapy and radiotherapy.

Central pathology review of the specimens was performed which included performing immunoperoxidase staining, and determining the mitotic index and tumour infiltrate lymphocytic density.

2.6 Follow up

Toxicity and clinical response were assessed weekly during radiation therapy and the courses of chemotherapy. Thereafter, reviews were conducted at minimum frequency of six monthly until death. Patients were discharged from follow-up after 5 years.

2.7 Outcome variables

The influence of PET on management was categorised by the treating oncologist, after the initial CT staging had been determined. Management impact was categorised into:

- High impact: the treatment aim changed from cure to palliation. Medium impact: method of treatment remained the same, but altered in extent or intensity.
- Low impact: the PET results had no change on the treatment aim, field size or dose.
- No impact: When the management plan was not changed despite being inconsistent with the post PET stage.

Pre-treatment FDG-PET scans were classified as a true positive (TP), true negative (TN), false positive (FP) and false negative (FN).by utilising the cytology results of FDG-avid tumour sites, and information from the week 12 post treatment clinical and PET assessment. If the cytology confirmed MCC then the patient was classified as TP. If the avid disease was negative on cytology or was consistent with other non MCC causes (eg sarcoid) then it was classified as FP. TN was defined as remaining free from progression clinically and on the post treatment PET. FN was defined as clinical or radiological progression up to the time of the post treatment PET. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio were then calculated.

2.7 Statistical methods

A generalised linear interactive modelling package (GLIM4) was used to examine the data. Overall survival considered any death as an event (including those from intercurrent illnesses). In-field Loco-regional control looked at the proportion who did not develop failure at the primary site, nodes or in-transit areas within the treated radiation volume, with censoring of events occurring at death without loco-regional

failure. Distant control was defined as the proportion of patients not developing haematogenous spread, with censoring occurring at death in the absence of distant failure. Cox's proportional hazards model was utilised to investigate the impact of prognostic variables on overall survival. Hazard ratios with 95% confidence limits were derived and P values were calculated.

3.0 Results

3.1 Patient characteristics

A total of 58 patients were recruited from 11 Australian institutions. Of these, 43 patients met eligibility criteria for treatment registration receiving chemo-radiotherapy as per protocol. No subjects were excluded from the analysis and none lost to follow-up. There were 45 males and 13 females with a median age of 68 years (range 26-84). Primary sites were head and neck in 12 cases, upper limb in 9, lower limb in 9 and trunk in 6, and unable to be identified in 22 cases. Approximately half the patients had gross residual disease at the primary site and/or nodes at the time of registration. 80% of patients with a known primary had a resection of macroscopic disease and 29% had nodal resections. Baseline subject characteristics is summarised in **Table 1.**

Subjects registered for treatment had pathologically involved nodes in 79.1% of cases and subjects had gross residual disease at the primary site and nodes in 14% and 51% of cases respectively prior to commencing chemo-radiotherapy. The patient characteristics are summarised in **Table 2**.

3.2 PET metrics

The impact of pre-treatment 18-FDG PET was classified as medium or high in 16 cases (27.6%) and had no or low impact in 42(72.4%) of cases. Upstaging was the most common outcome occurring in 15(25.9%) of cases and there were no cases of downstaging. Upstaging was due to the detection of distant metastases (4 cases) or regional nodes (6 cases) that were not reported on the CT. There were no cases where an occult skin primary was found on the PET. Other non-related malignancies and benign conditions such as sarcoid were diagnosed in 4(6.9%) of cases.

Cytology was performed on avid sites in the primary in 12 cases, nodes in 32 and distant sites in 5 cases. This was positive for MCC in 10(83%), 31(96%) and 3(60%) cases respectively.

Of the 58 pre-treatment 18-FDG-PET scans, there were 36 true positives, 15 true negatives, 2 false negatives and 2 false positives. This resulted in a sensitivity of 94.7% (95% CI 82-99.3%) and a specificity of 88.2% (95% CI 63.6-98.5). The positive predictive value was 94.7% (83.01-98.1) and the negative predictive value was 88.2% (95% CI 65.8-96.6). The positive likelihood ratio was 8.05 (95% CI 2.2-29.7) and the negative likelihood ratio was 0.06 (95% CI 0.02-0.23). This is summarised in **Table 3.**

There was 95% compliance with performing a post-treatment PET which was undertaken in 41 cases. Complete metabolic response (CMR) occurred in 36 (87.8%) of cases. Residual activity was present in the primary site in 2(4.8%) cases, regional nodes in 3(7.3%) cases and distant disease in 3(7.3%) cases. The mean SUV max in the post-treatment PET was 2.07 compared to 7.52 in the pre-treatment PET.

3.3 Survival analyses

The close out date for analysis was January 2017 and all survival calculations were from the date of registration. The median potential follow-up was 44.9 months (95% CI 39.7-51.1). The 3-year overall survival was 76% and the 3 year in-field loco-regional control was 89%. The 3-year distant control was 70%.

3.4 Univariate analysis

A univariate analysis was undertaken for prognostic variables using overall survival as an endpoint. The presence of nodal disease increased the risk of death by approximately three times, but this did not achieve statistical significance (HR =2.89, p=0.32). Pre-treatment lesion SUVmax uptake levels had no demonstrable impact on overall survival (HR=0.94 p=0.37). The status of the post treatment PET also had no impact on survival (HR=0.55 p=0.35). These results are summarised in **Table 4**.

4 Discussion

This prospective study confirms the utility of PET in staging patients with MCC. A medium to high impact on management occurred in 27.6% of cases which is similar to that reported by Siva et al in 2013 where PET altered the management in 37% of cases. [9] The difference may be due to more rigorous screening of patients in a clinical trial compared to a retrospective study as well as the exclusion of patients with immunosuppression. The impact of PET was largely due to upstaging of disease which occurred in 25.9% of patients. The detection of new sites of nodal involvement (6 cases) is slightly more common than the detection of new sites of distant metastatic disease (4 cases). Both these scenarios will have significant impact on management PET was useful in determining the extent of involved nodes which is fundamental to accurate volume definition in planning. Failure to include all the involved nodes will result in loco-regional failure and increase the risk of distant failure. The presence of metastatic disease will change the treatment aim from cure to palliation with the main treatment modality systemic in the form of chemotherapy or immunotherapy. In a large series of 61 patients reported by Hawryluk, et al, Stage III patients were upstaged in 16% of cases.[10] In addition it is well recognised that PET staging may detect other malignant diseases of which the patient may have been unaware. The impact of this remains uncertain.

This impact of PET on early stage disease cannot be confirmed from this study as this study only included high risk patients in the treatment registration cohort. There were only 9 patients with primaries larger than

2cm without pathologically involved nodes (Stage IIA). Patients with early stage disease are less likely to benefit from the routine use of PET as their risk of nodal disease and distant metastatic disease is lower than this cohort of patients who were defined as high risk. In this setting, sentinel lymph node biopsy may have a greater impact on management than PET.[11]

MCC is an aggressive tumour with high glucose uptake. The mean lesion SUV values in other series have varied from 4.9-7.2.[9, 10] This compares with the mean SUV of 7.52 in this study. In the Siva et al series, there was no adverse impact on survival associated with increasing SUV values alone.(9) We also were unable to demonstrate a relationship between increasing SUV uptake and survival but the small number of patients precludes any definitive conclusions.

We did not find that a positive post-treatment PET had any demonstrable impact on 3-year overall survival, but this may relate to the small number of patients with a positive PET and potentially the early intervention with salvage surgery for loco-regional failures. Of the 5 patients with positive post-treatment PET scans, 2 of the patients had loco-regional relapse and were potentially salvageable and the remainder had distant disease and were deemed incurable. The overall complete metabolic response (CMR) was 87.8% indicating a high level of efficacy. This figure reflects the in-field control rates we expect with contemporary chemo-radiotherapy, even though the dose for macroscopic disease was limited to 54Gy. This does suggest that weekly carboplatin has resulted in some degree of radiosensitization. In other larger studies, CMR is highly prognostic for survival with a 68% 5-year survival compared to 15% 1 year survival in those who did not achieve it. In addition, restaging PET had a high and medium impact on management in 45% and 11% respectively.[12] Assessing the burden of metastatic disease may be important in the context of the recent trials with high response rates using where control varies with burden of metastatic disease.[13] Further research into the areas of early detection of metastatic disease and assessment of disease burden in the era of immunotherapy are required.

The strength of the TROG 09:03 study lies in the prospective staging of patients and categorisation of the impact on management. This has been extensively reported by others but these studies have been retrospective with the potential for investigator bias.[6, 14-18]. A systematic review and meta-analysis was performed in 2013 on 10 studies compromising 329 patients and 549 scans. A detailed quantitative analysis on 92 patients confirmed a sensitivity of 90% (95% CI 80-96) and specificity of 98% (95% CI 90-100). The positive likelihood ratio was 12% (95% CI 4.3-33) and negative likelihood ratio was 0.15 (95% CI 0.08-0.28).[7]

The impact on management was determined by the treating oncologist and not by independent review and this is a potential cause of bias. The treating oncologist would have access to the complete clinical story including CT scans, reports, clinical correlation, and cytological and pathology reports.

Doses of 50Gy are effective for microscopic disease but dose greater than 55Gy are required for gross disease.[19] The selection of the radiation dose was influenced on being able to give a dose protocol that was deliverable across multiple tumour sites, large treatment volumes with bolus and multiple treatment institutions. A dose of 54Gy for macroscopic disease and 50Gy for microscopic disease was chosen as being a safe in conjunction with chemotherapy. The 3-year in field loco-regional control rate of 89% was high given that 14% had gross residual disease at the primary site and 51.2% at the nodal site. This adds further weight to the argument that wide potentially morbid resection of MCC prior to radiation treatment is not required and high levels of in-field control of 75-89% can be achieved with radiation alone.[20, 21] Compared to historic series treated in the pre-PET era where 5 year survival rates of 40-64% were the norm, these results are encouraging.[22-25]

This prospective phase II study of MCC demonstrates that pre-treatment PET can have a moderate to high impact on management in approximately one third of cases. No prognostic impact related to SUV or post-treatment PET was detected but his may have been limited by the small numbers in the series. The sensitivity and specificity of 18-FDG PET/CT in MCC is high suggesting that it should be considered prior to embarking on treatment.

At the present time in Australia, 18-FDG PET/CT scans for MCC are not eligible for reimbursements under the Medical Benefits Schedule. This study provides some justification for considering pre-treatment PET in Stage III patients. The impact of PET for Stage II patients remains questionable. Likewise, the routine use of post-treatment PET requires further investigation. Further research into PET with cost metrics endpoints need to be done to better define the economic impact.

Acknowledgements

This research was funded by Cancer Australia for which we are enormously grateful. The support of the Trial Management Committee and the TROG office is also recognised. We would like to acknowledge Prof Jane Armes who reviewed the pathology and Kacy Baumann, Adrienne See and Narelle Wallace from the ROPART Trials office, without whose attention to detail and dedication to their work, this research would not have been possible. The participating centres were Radiation Oncology Princess Alexandra Hospital, Peter MacCallum Cancer Centre, Royal Prince Alfred, Calvary Mater Newcastle, Liverpool, Royal Brisbane and Women's Hospital, Radiation Oncology Centres, Genesis, Geelong and Westmead Hospitals.

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Table 1

Patient characteristics of all patients

Characteristics of whole group		Number (n=58)	%
Age		Mean 68 (26-84)	
Gender			
	Male	45	77.6
	Female	13	22.4
Site of primary			
	Occult	22	37.9
	Lower limb	9	15.5
	Upper limb	9	15.5
	Head and neck	12	20.7
	Trunk	6	10.3
Gross Residual Disease			
	Nil	30	51.7
	Nodes	21	36.2
	Primary	3	5.2
	Primary & nodes	4	6.9
	Primary median diameter (mm)	21(5-40)	
	Nodal median diameter (mm)	29(1.3-40)	
T stage			

	T0	22	37.9
	T1	22	37.9
	T2	14	24.1
N stage			
	N0	18	31.0
	N1	40	69.0
TREATMENT			
Primary surgery			
	Clear margins	8	13.8
	Close margins	3	5.2
	Positive margins	18	31.0
	Gross Residual	6	10.3
	Occult	22	37.9
Nodal surgery			
	Nil	18	31.0
	Sentinel node biopsy	2	3.4
	Biopsy	19	32.8
	Nodectomy	1	1.7
	Nodal dissection	17	29.3
	Unknown	1	1.7

Chemotherapy	
Carboplatin median dose (mg)	343 (110-696)
Etoposide median dose (mg)	160 (112-167)
Radiation	
Median dose to primary (Gy)	51.5 (51.2-52.7)
Median fractions to primary	26 (25-30)
Median dose to nodes (Gy)	50 (20-60)
Median fractions to nodes	25 (25-33)

Table 2

Patient characteristics of patients completing chemo-radiotherapy and post treatment PET.

Characteristics of C/RT group	**n=43**	
%Age	65 (26-84)	
Gender		
Male	33	76.7%
Female	10	23.3%
Site of primary		
Occult	19	44.2%
Lower limb	5	11.6%
Upper limb	6	14.0%

	Head and neck	9	20.9%
	Trunk	4	9.3%
Gross Residual Disease			
	Nodes-yes	22	51.2%
	-no	12	27.9%
	Unknown	9	20.9%
	Primary- yes	6	14.0%
	-no	20	46.5%
	Unknown	17	39.5%
	Mean size of gross disease (mm)	23.8	
T stage			
	T0	19	44.2%
	T1	14	32.6%
	T2	10	23.3%
N stage			
	N0	9	20.9%
	N1	34	79.1%
Post Treatment PET			
	Negative	36	87.8%
	Positive	5	12.1%
Tumour Mitotic Index			
	0-5	18	41.9%

	6 to 10	8	18.6%
	>10	13	30.2%
	Unknown	4	9.3%
Tumour Infiltrating lymphocyte density			
	Absent	14	32.6%
	<1/3	23	53.5%
	>=1/3-2/3	2	4.7%
	Unknown	4	9.3%

Table 3

PET related endpoints

Impact of PET			
	No impact	1	1.7%
	Low	41	70.7%
	Medium	10	17.2%
	High	6	10.3%
Influence of PET			
	Upstaged	15	25.9%
	Down staged	0	0.0%
	Other diseases	4	6.9%
	None	39	67.2%

True positives	36	62.1%
True negatives	15	25.9%
False negatives	2	3.4%
False positives	2	3.4%
Unknown	3	5.2%
Sensitivity	94.74 (82-99.3)	
Specificity	88.24 (63.56-98.54)	
Positive predictive value	94.74 (83.01-98.51)	
Negative predictive value	88.24 (65.81-96.69)	
Positive Likelihood Ratio	8.05 (2.19-29.67)	
Negative Likelihood Ratio	0.06 (0.02-0.23)	
Mean SUV max pre treatment	7.52	
Mean SUV max post treatment	2.07	

Table 4

Univariate analysis of prognostic factors in the 43 patients completing chemo-radiotherapy, using overall survival as the endpoint.

FACTORS	95% CI	HAZARD	P
Age	0.99-1.14	1.06	**0.1**
Gender: male vs female	0.15-3.41	0.72	**0.68**

Primary site: occult vs others	0.31-3.86	1.09	**0.9**
T stage: T0 vs T1	0.31-4.95	1.24	**0.76**
vs T2	0.16-4.81	0.88	**0.88**
N stage: N0 vs N1	0.37-22.82	2.89	**0.32**
Gross Disease at primary: no vs yes	0.00-395414334426	0.00	**0.66**
Gross Disease at nodal: no vs yes	0.24-3.34	0.89	**0.87**
Pre-treatment SUV	0.82-1.08	0.94	**0.37**
Mitotic Index: 0-5 vs 6-10	0.14-3.64	0.70	**0.67**
vs >10	0.19-3.35	0.80	**0.76**
Tumour infiltrate lymphocyte density:			
absent vs <1/3	0.12-1.44	0.41	**0.17**
vs 1/3 to 2/3	0.00-914583093668450000000	0.00	**0.78**
Post treatment PET: neg vs pos	0.15-1.95	0.55	**0.35**

Figure 1: 3 year in-field loco-regional control for patients completing chemo-radiation.

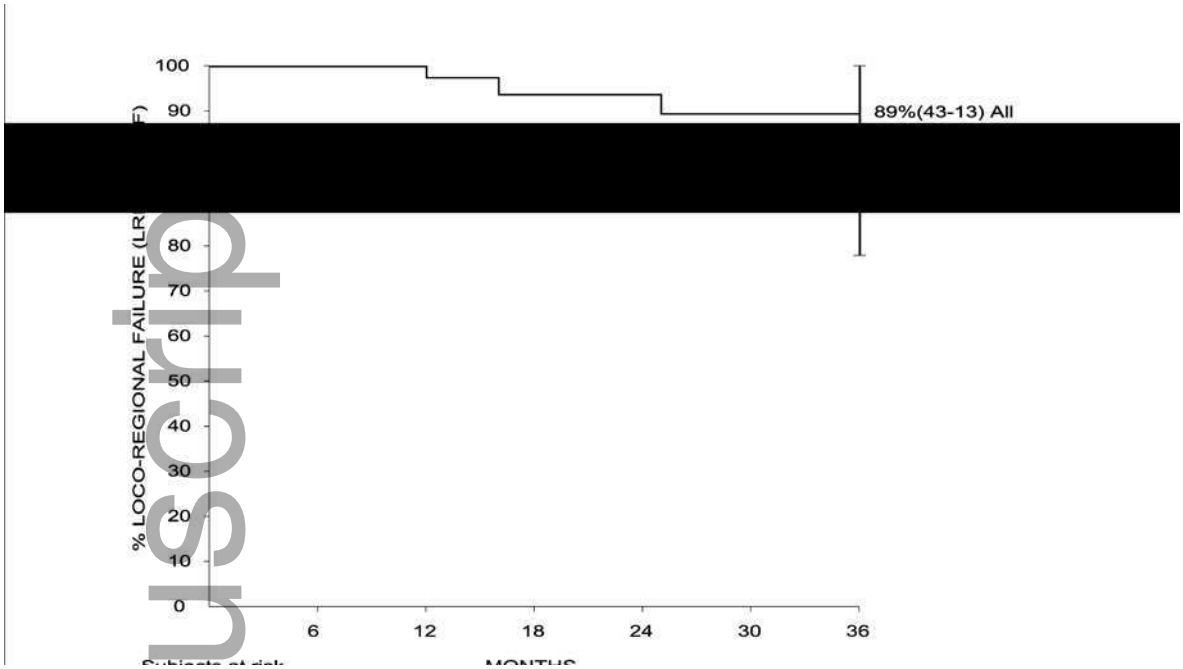

Figure 2

3 year overall survival for patient completing chemo-radiotherapy.