Stereotactic Ablative Body Radiotherapy for Inoperable Primary Kidney Cancer: A Prospective Clinical Trial

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Abstract:

Objective: To assess the feasibility and safety of stereotactic ablative body radiotherapy (SABR) for RCC in patients unsuitable for surgery. Secondary objectives were to assess oncologic and functional outcomes.

Materials and Methods: This was a prospective interventional clinical trial with institutional ethics board approval. Inoperable patients were enrolled after multidisciplinary consensus for intervention and informed consent. Tumor response was defined using RECIST 1.1 criteria. Toxicities were recorded using CTCAE v4.0. Time-to-event outcomes were described using Kaplan-Meier method and associations of baseline variables with tumor shrinkage was assessed using linear regression. Patients received either single fraction of 26Gy or three fractions of 14Gy dependent on tumour size.

Results: Of 37 patients (median age of 78 years), 62% had T1b, 35% had T1a and 3% had T2a disease. One patient presented with bilateral primaries. Histology was confirmed in 92%. In total 33 patients and 34 kidneys received all prescribed SABR fractions (89% feasibility). The median follow-up was 24 months. Treatment related grade 1-2 toxicities occurred in n=26 (78%), grade 3 toxicity in n=1 (3%). No grade

4-5 toxicities were recorded and n=6 (18%) reported no toxicity. Freedom from local progression, distant progression and overall survival at 2 years were 100%, 89% and 92%, respectively. The mean baseline GFR was 55 mL/min, which decreased to 44 mL/min at 1 and 2 years ($p < 0.001$). Neutrophil to lymphocyte (N/L) ratio was correlated to % change in tumor size at 1-year, $r^2=0.45$, $p<0.001$.

Conclusion: SABR for primary RCC is feasible and well tolerated. We observed encouraging cancer control, functional preservation and early survival outcomes in an inoperable cohort. Baseline N/L ratio may be predictive of immune-mediated response and warrants further investigation. Limitations include lack of long-term oncologic and functional outcomes.

Key words: ablation, clinical trial, nephron sparing, SBRT, radiation, renal cell carcinoma,

Introduction;

Renal cell carcinoma (RCC) is the 8th most common cancer worldwide [1] and continues to increase in incidence and lethality. According to the American Cancer Society, kidney cancer incidence rates increased by 4.1% per year in men and 3.3% per year in women between 2004 and 2008 [2]. Surgery is the standard of care for primary RCC. However, many patients are in an older age group [3] and have associated medical comorbidities that may preclude them from extirpative therapies. Patients undergoing partial or radical nephrectomy experience post-operative nephron loss, which may result in de novo chronic kidney disease or advancement of pre-existing renal dysfunction [4].

Non-surgical definitive treatment options for this population of patients are limited. Radiofrequency ablation (RFA) and cryotherapy are two common thermal ablation techniques that have specific limitations. They are typically limited to small renal masses and are generally restricted to lesions located away from the ureter and vascular structures due to the risk of heat sink effects, stricture and/or fistula development [5]. With larger tumours there is a significant risk of haemorrhage, which can require major intervention to control. Both of these techniques are invasive adding to complication risk and issues with managing anticoagulative medications.

In contrast, SABR is a non-invasive treatment option for patients deemed unsuitable for surgical intervention. SABR is delivered to patients whilst fully awake and in a single or few outpatient treatment sessions. SABR is well established in the treatment of cancers in the lung, liver and spine. Whilst the approach is still emerging in the kidney, it is not technically limited by tumour proximity to central pelvic-calyceal structures or to small renal masses [6]. However there is a paucity of prospective data to support the routine adoption of SABR for primary inoperable RCC [7]. In this context we conducted a prospective clinical trial of SABR for this disease setting. The primary purpose of the study was to assess the feasibility and safety of this approach using conventional linear accelerators without fiducial marker insertion, an approach readily translatable to radiotherapy departments worldwide.

Materials and Methods;

Patient population:

This was an institutional ethics board approved single institutional prospective clinical trial (clinicaltrials.gov ID NCT01676428) conducted at the Peter MacCallum Cancer Centre. All patients signed informed consent. Eligible patients were enrolled between 2012 and 2014 and were aged > 18 years, ECOG performance of 0-2 inclusive and had a single lesion within the target kidney. Patients were medically inoperable, high-risk for surgery (due to likelihood of post-surgical dialysis) or refused surgery. Patients were excluded when receiving systemic therapy prior to or concurrent with SABR, or when having previously received high-dose radiotherapy to the upper abdomen. Biopsy confirmation was attempted in all patients when possible. Patients with small renal masses (T1a disease) were evaluated closely for the need for treatment factoring for existing comorbidites; these patients had documented growth on serial imaging, and/or symptomatic with haematuria or pain. Multidisciplinary tumour board consensus was required before active intervention was recommended. Bloods were taken for haematology (including neutrophil and lymphocyte count) and electrolyes (including creatinine) at baseline and at each clinical visit.

Study objectives:

The primary objective was to assess the feasibility of treatment as defined by successfully delivering the treatment plan as prescribed and achieving the nominated dose constraints. Secondary objectives were to assess; (a) treatment related adverse events, (b) freedom from local progression (c) freedom from distant progression and (d) overall survival. A further exploratory objective was to identify possible predictors of change in tumour size after 1 year of SABR.

Study protocol:

Trial investigations occurred 3 monthly after treatment with data close-out after all patients completed a minimum of 12 months potential follow-up. Investigations included serum urea and electrolytes and estimated glomerular filtration rate (eGFR) using CKD-EPI formula calculations, CT of the chest and abdomen and clinical

review with adverse event reporting. All RECIST tumour measurements were performed by a single experienced radiologist (TT).

For primary RCCs of <5 cm in maximal dimension a single treatment of 26 Gy was delivered. For RCCs of ≥ 5 cm in maximal dimension 42Gy in 3 fractions was delivered on non-consecutive days. All treatments were delivered on conventional c-arm linear accelerators, either Varian Truebeam STx or Trilogy (Varian, Pal Alto, California). All patients were immobilised using an Elekta Bodyfix dual vacuum device (Medical Intelligence, Schwabmünchen, Germany). Radiotherapy treatment delivery techniques have been previously described in detail [8]. The motion encompassing internal target volume (ITV) was constructed using four-dimensional CT simulation. A 5mm expansion was given to derive the planning target volume. The peak dose within the ITV was typically 125% of the prescribed dose, with target coverage of the PTV being 95%-99% by the prescription isodose.

Statistical Methods:

Patient demographics, baseline characteristics and treatment details were described using descriptive statistics. Ninety-five percent exact two-sided confidence intervals were used to assess the primary objective of feasibility. Treatment related toxicities were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Toxicities were reported separately for the acute period (up to 90 days from SABR treatment) and late period (beyond 90 days from SABR treatment). Freedom from local progression (FFLP), freedom from distant progression (FFDP) and overall survival (OS) were estimated using the Kaplan-Meier method with corresponding 95% confidence intervals. FFLP, FFDP and OS were calculated from the date of first SABR treatment. Local progression was defined using Response Evaluation Criteria In Solid Tumors v1.1 (RECIST[9]). The percentage change in tumour size (maximum diameter in AP and transverse directions) and volume from baseline was calculated for each CT assessment. Linear regression was used to assess candidate prognostic variables (histological grade, target volume, dose and neutrophil : lymphocyte ratio) for change in tumour size from baseline to 1 year after SABR.

The proportion of patients who developed new onset chronic kidney disease (CKD), as defined by eGFR < 60mL/min, was described. Estimate of change in eGFR in 1 year with 95% confidence interval was provided from a linear mixed model with time as a fixed effect and patient as a random effect. This process was repeated for the subset of patient with/without pre-existing chronic kidney disease and by number of risk factors for chronic kidney disease. Average GFR loss from baseline to 1 and 2-years was estimated with 95% confidence intervals.

Results;

In the 2-year accrual period 37 eligible patients signed informed consent. These patient characteristics can be found in **Table 1**. T1a disease accounted for 35% of cases, with T1b in 62% and T2a in 3%. Histological confirmation was achieved in 92% of kidneys (n = 34). Of these cases, tumour necrosis in the pathological specimen was noted in 33 (97%), and no cases demonstrated sarcomatoid differentiation. Medical risk factors for chronic kidney disease (CKD) included diabetes in 14 (38%), hypertension in 24 (65%) and cardiovascular disease in 19 (51%). The Charlson comorbidity score was 6 or greater in 28 patients (76%), with 11 patients referred due to being technically high risk of post-surgical dialysis (30%) with a complex tumour in a dominant functioning kidney. Only one patient in the cohort refused surgery as the reason for enrolment (Charlson score 1).

Of the 37 patients who fulfilled eligibility criteria, 33 patients received all study treatments to 34 primary RCCs resulting in a feasibility rate of 89% (95% CIs [73% - 94%]). Of the 4/37 patients for which treatment was not delivered, one died after an international flight with a pulmonary embolus prior to SABR and two could not meet planned dose constraints. One further patient completed only two of three planned fractions due to social difficulties , Acute and late treatment related toxicities are demonstrated in **Table 2**. One patient (3%) had a treatment related grade 3 toxicity (fatigue), 26 (78%) reported grade 1-2 treatment related toxicity as worst grade and 6 patients (18%) reported no treatment related side-effects. There was no treatment related mortality, and no grade 4 toxicities were recorded.

Radiotherapy treatment characteristics were as follows; 17 patients were prescribed 26Gy in a single fraction and 17 were prescribed 42Gy in three fractions. For single fraction and three fraction SABR, the PTV volume was a median [interquartile range (IQR)] of 77.2cc [51.8 - 89.4] and 166.8cc [133.1 - 214.2], respectively. The mean PTV dose as a percentage of the prescription dose was a median [IQR] of 122% [117 - 124] and 117% [110 - 120], respectively. The minimum PTV dose as a percentage of the prescription dose was a median [IQR] of 92% [88 - 96] and 81% [58 - 93], respectively.

Oncologic outcomes are depicted in **Figure 1** and **Figure 2**. The FFLP at 1 and 2 years was 100%. One patient progressed locally with concurrent distant progression at 28 months post-treatment. FFDP at 1 and 2 years was 97% (95%CIs [91-100]) and 89% (95%CIs [78-100]), respectively. One and two year OS was 100% and 92% (95%CIs [81-100]), respectively. At last follow-up, 4 patients had partial responses and 28 had stable disease as defined by RECIST criteria. Objective tumor size reduction at 1-year was observed in 61% of RCCs after SABR. In the univariate analysis describing % change in tumour size from baseline to 1-year (**Table 3**), only a lower N:L ratio was significantly associated with tumour shrinkage ($r^2 = 0.45$, $p < 0.001$). A representative image of tumour shrinkage after therapy is depicted in **Figure 3**.

The baseline mean eGFR was 55 mL/min (range 18 to 97). At 1-year the eGFR was reduced by 11 mL/min (95% CI [6 to 17]), and in the subset of nine patients who were assessed at 2-years, there was a similar reduction from baseline by 11 mL/min (95% CI [3 to 19]). Whilst the change in eGFR was statistically significant at 1-year ($p<0.001$) using linear mixed models, the slopes of change in eGFR on patient with pre-existing CKD were not different from patients without pre-existing CKD (difference in slopes of -2.1 mL/min, 95% CI [-5.3 to 1.1], $p = 0.196$). The slopes by the number of risk factors for CKD was also not statistically significant ($p = 0.536$).

Discussion

This study has demonstrated the safety and efficacy of a conventional linear accelerator based technique for the treatment of primary inoperable RCC. The majority (65%) of tumours treated were large renal masses (> 4cm). We observed grade 3 toxicity rates of 3% (transient fatigue) and no grade 4-5 toxicities. Importantly, most patients sustained only transient minor side effects (78%) or no-treatment related side effects (18%). Freedom from local progression at 2 years was 100%, with FFDP and OS being 89% and 92% respectively. These results compare favourably with the existing largely retrospective literature suggesting local control rates ranging between 84%-100%, with similarly low rates of associated toxicity [10]. A recent prospective phase I trial of 19 patients and a prospective series of 29 patients with primary RCC [11, 12] corroborate the findings of infrequent treatment related side effects (< 5% grade 3+ toxicities). Most of the existing literature is from groups using the Cyberknife™ (Accuray, Sunnyvale CA), a specialised robotic stereotactic radiotherapy delivery system. This system necessitates the insertion of fiducial markers for tumour tracking, an intervention that is invasive and associated with the risk of tumour haemmorhage. Importantly, our results were derived using conventional radiotherapy linear accelerators that are ubiquitous in modern radiotherapy departments worldwide, lending credence to the generalizability of our results internationally.

The majority (65%) of patients treated in our cohort had primary RCC larger than 4cm in size. A major advantage of SABR over thermal ablation is the capacity to treat larger masses, as RFA and MWA are typically limited to the treatment of smaller small renal masses (< 4cm). Whilst cryotherapy has the capacity to treat larger tumours, both complication rate and efficacy appear to be reduced. A multivariable analysis of outcomes in 99 patients undergoing laparoscopic cryoablation from the Netherlands determined that whilst lesion complexity did not prognosticate for risk of complications, tumour size > 3.5cm did [16]. Tumour control also appears to correlate to size, with a series of 124 patients from Washington University [17] of percutaneous cryoablation reporting a 2-year disease free survival of 85%, with tumour size > 3cm being predictive of recurrence on multivariable analysis. Overall, one meta-analysis [18] reported a similar proportion of clinical efficacy for cryoablation at 89% versus RFA at 90%, whilst another [19] suggested better local tumor control of 94.8% after

cryoablation compared to 87.1% after RFA. These rates are comparable to that of our series (despite the treatment of T1b and T2 disease) and other literature of SABR for primary RCC [10]. Importantly SABR can be protocolized and is thus not dependent on technician experience or learning curve, increasingly the likelihood of reproducibility outside of major academic centres.

An important consideration of ablative interventions for primary RCC is the ability to conserve nephrons and renal function. At last recorded clinical visit up to three years after SABR, no patient required renal replacement therapy. Both SABR and thermal ablative techniques affect a rim of surrounding normal kidney [20, 21]. Meaningful comparisons are particularly challenging, as resultant renal dysfunction is proportional to tumor size and volume of ablation zones [22]. Most series of thermal ablation report outcomes from only small renal masses of typical average sizes ranging 2-3 cms in diameter, with very limited prospectively collected renal function outcomes. In one prospective study of 102 patients randomised to microwave ablation (MWA) versus partial nephrectomy (PN), the mean tumour size was 3.1 cms and 2.8 cms, respectively. The mean eGFR for the MWA arm dropped by 7mL/min from a baseline value of 130 mL/min, and dropped by 25 mL/min from a baseline value of 113 mL/min in the PN arm [23]. In a further study of 541 patients of randomised between radical nephrectomy (RN) and partial nephrectomy (PN) [24], the median tumour size was 3.0 cms. During the first year after surgery, mean eGFR was 52.7 mL/min in the RN arm and 66.8 mL/min in the PN arm. The proportion reaching a post-operative eGFR was < 60 mL/min was 85.7% with RN and 64.7% with PN. By comparison, the median tumour size treated in this trial was 4.8cm, and the mean pre-treatment eGFR was already significantly impaired at 55 mls/min. The average post-treatment reduction was to 44 mls/min, and no patient required dialysis. In the 14 patients with an initial eGFR of > 60mL/min, new onset eGFR of < 60mL/min occurred in 10 (71.4%). Importantly this proportion of new onset CKD was similar to that of PN in the surgical series discussed above (64.7%), and lower than that of RN (85.7%) [24]. Our cohort had significant medical risk factors for CKD, including diabetes in 38%, hypertension in 65% and cardiovascular disease in 51%. Thus, whilst it is difficult to compare treatment approaches given the differences in tumour size, patient comorbidities and pre-existing renal dysfunction, in the context of the

alternative therapeutic interventions of surgery and thermal ablation we observed a comparable and clinically acceptable preservation of renal function after SABR, consistent with previous reports [11, 12].

An exploratory finding of this study was the inverse correlation observed between N:L ratio and tumour response to SABR. Raised levels of circulating neutrophils in peripheral blood is considered to be a biomarker of a chronic inflammatory state within the host, whilst depressed lymphocyte levels are considered to be reflective of a reduced capacity to mount an inflammatory response to cancer [25]. Although it is recognised that SABR is a highly effective at RCC control in preclinical [26] and clinical studies [27], this efficacy may not be solely attributable to higher biological radiation dose. Indeed, it is possible that some of the efficacy of SABR is directly attributable to immune stimulating properties [28]. RCC is a highly immunogenic tumour that has shown impressive responses to immunotherapy [29] as well as 'abscopal' or out-of-field distant tumour responses to radiotherapy with or without immunotherapy [28]. It may be that the association between lower N:L ratio and tumour shrinkage is a correlate of lymphocyte mediated adaptive immune response in the irradiated primary. This suggests possible utility as a novel and easily accessible predictive biomarker of response to therapy in patients undergoing SABR for primary RCC. This finding warrants further investigation and validation in future studies.

Radiological response assessment after SABR using CT criteria represents several challenges. Post-ablative radiotherapy effects in the tumour and adjacent normal tissues can evolve over years [13], and in the more common application of SABR for lung tumours, functional imaging with positron emission tomography (PET) can detect metabolic responses that long predate any CT apparent morphological changes [14]. However, PET imaging does not have an established role in the context of primary RCC. Presence of tumour cells on biopsy after ablative radiation can also be unreliable, such as in the context of prostate brachytherapy, where positive biopsies can occur up to 2-years post-therapy but does not correlate to biochemical disease control [15]. Whilst residual post-radiation tissue within the treated field is expected, tumour progression on CT imaging is not, and thus progression is typically used as a surrogate for treatment failure.

This study has several limitations. First and foremost, since this is an early phase clinical trial, longer-term follow-up is required to establish robust efficacy outcomes in this cohort. Secondly, the treatment of small renal masses may be criticised by some with expected growth rates of 0.25cm per year [30] and low metastatic potential [31]. As described the patients in this study had already demonstrated progression and/or symptoms after initial active surveillance and treatment was recommended only once co-morbidities had been carefully balanced by a multidisciplinary tumour board. Furthermore the vast majority included in this study were larger masses indicating the feasibility of SABR in masses not amenable to thermal ablative techniques. Additionally, histological confirmation was not achieved in all cases (8%). Finally, the observed post-treatment decline in GFR was modest but again longer data would be reassuring in order to evaluate functional outcomes.

Conclusions;

SABR for both small and large primary RCC is well tolerated. We observed encouraging cancer control, functional preservation and survival in an inoperable cohort. Baseline N/L ratio may be predictive of immune-mediated response and warrants further investigation. The findings of this study have been used to inform the design of an international phase II clinical trial under the auspices of the TransTasman Radiation Oncology Group (TROG 15.03 FASTRACK, clinicaltrials.gov ID NCT02613819). This study is designed with the purpose of validating the efficacy of our treatment technique in a multi-institutional setting.

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Table and Figure Legends

Figure 1 – Time to local progression at per patient level

Figure 2 – Overall survival (panel A), and freedom from distant progression (panel B). Dashed lines represent 95% confidence intervals.

Figure 3 – Representative image depicting maximal dimensions of a right sided Fuhrman grade 2 primary RCC at baseline (left) and 1-year post SABR (right), demonstrating typical appearance of tumour shrinkage without change in contrast enhancement characteristics.

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Table 1: Patient characteristics

Variable	Statistic / level	Count (%)
Age (years)	Median [range]	78 [42 - 91]
Sex	Female	9 (24%)
	Male	28 (76%)
T stage	1a	13 (35%)
	1b	23 (62%)
	2a	1 (3%)
Tumour size largest dimension (mm)	Mean (SD)	49.2 (12.6)
	Median [range]	48 [21 - 75]
Neutrophil:lymphocyte ratio (baseline)	Mean (SD)	4.6 (6.5)
Laterality	Bilateral	1 (3%)
	Left	18 (49%)
	Right	18 (49%)
Histological grade	I	3 (9%)
	II	20 (59%)
	III	1 (3%)
	Not otherwise specified	10 (29%)
Histological subtype	Clear Cell	30 (88%)
	Mixed	1 (3%)
	Papillary/Chromophilic	3 (9%)
Diabetes	No	23 (62%)
	Yes	14 (38%)
Hypertension	No	13 (35%)
	Yes	24 (65%)
Cardiovascular disease	No	18 (49%)
	Yes	19 (51%)
Charlson score	1-2	2 (5%)
	4-6	7 (19%)
	6	7 (19%)
	7	9 (24%)
	8	6 (16%)

Table 2: Treatment related adverse events according to period (acute and late) and overall

	Acute (≤90 days post SABR)			Late (>90 days post SABR)			Overall		
Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
Abdominal pain	0	0	0	0	1	0	0	1	0
Back pain	0	0	0	0	0	0	0	0	0
Chest Wall Pain	5	0	0	12	0	0	15	0	0
Dermatitis	2	0	0	0	0	0	2	0	0
Diarrhoea	3	0	0	1	0	0	3	0	0
Dizziness	0	0	0	0	0	0	0	0	0
Dizzy	0	0	0	0	0	0	0	0	0
Dyspnoea	0	1	0	2	0	0	2	1	0
Fatigue	11	6	0	7	0	1	14	5	1
Gastritis	1	1	0	1	0	0	2	1	0
Haematuria	0	0	0	3	1	0	3	1	0
Left flank pain	0	0	0	0	0	0	0	0	0
Nausea	5	2	0	2	0	0	5	2	0
Pneumonia	0	0	0	0	0	0	0	0	0
Right Flank Pain	1	0	0	0	0	0	1	0	0
Skin induration	0	0	0	1	0	0	1	0	0
At least one event (%)	**11(33%)**	**7(21%)**	**0**	**17(52%)**	**2(6%)**	**1(3%)**	**19(58%)**	**7(21%)**	**1(3%)**

Table 3: Univariate analysis of % change in tumour size from baseline to 1 year post SABR.

Variable	Mean ± SD	r^2	Coefficient ± SE	p-value
Histological grade				0.318
NOS and I	-4.22 ± 9.38		1	
II and III	-9.07 ± 13.43		-4.84 ± 4.73	
Minimum target dose (%)		0.02	-0.10 ± 0.14	0.475
Mean target dose (%)		0.01	-0.16 ± 0.26	0.551
PTV volume (cc)		0.01	0.02 ± 0.03	0.627
Baseline tumour volume		0.00	-0.02 ± 0.64	0.806
Neutrophil/Lymphocyte ratio		0.46	4.67 ± 1.02	<0.001

NOS = not otherwise specified, cc = cubic centimetres

Figure 1

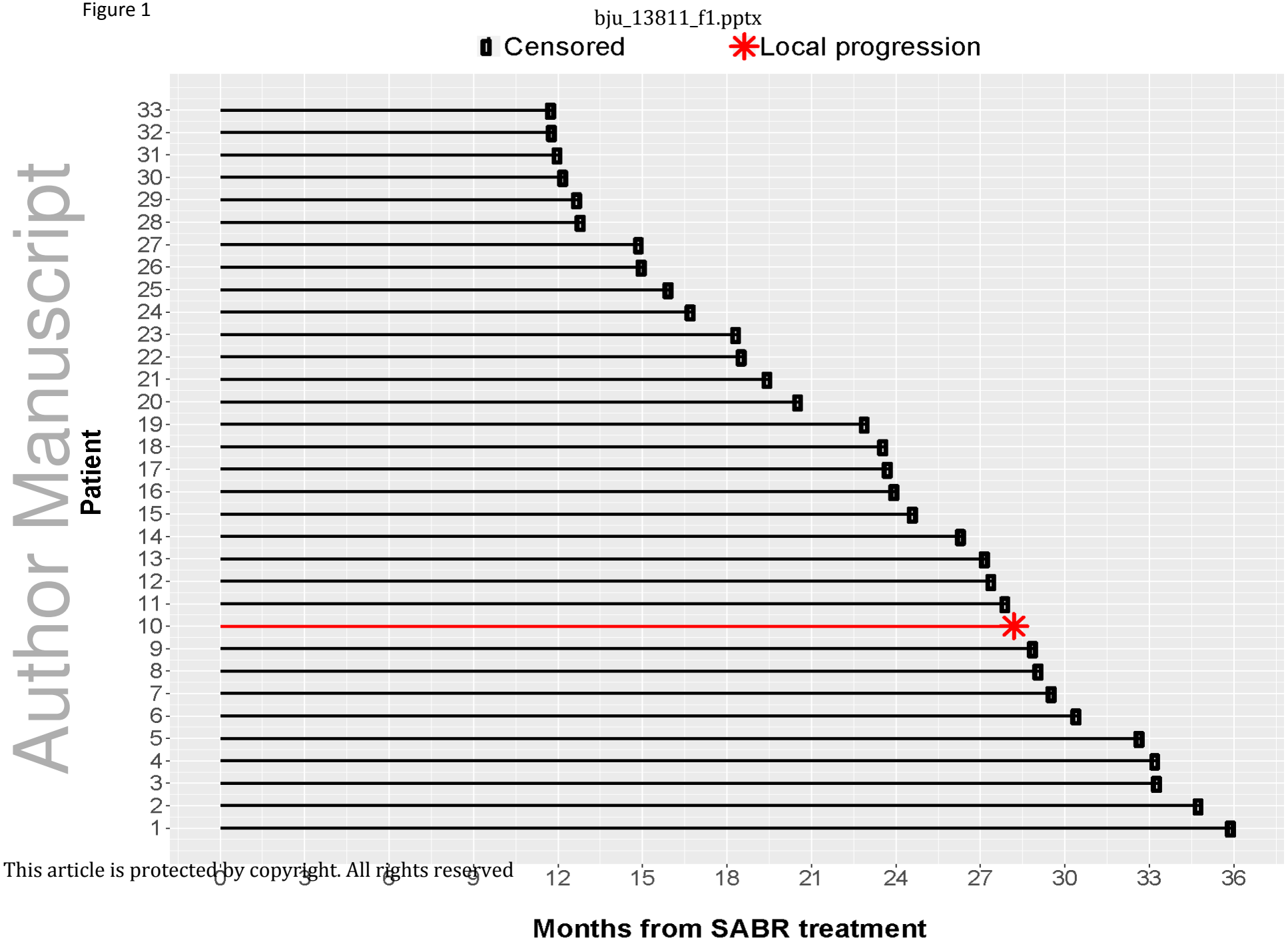

Figure 2

bju_13811_f2.pptx

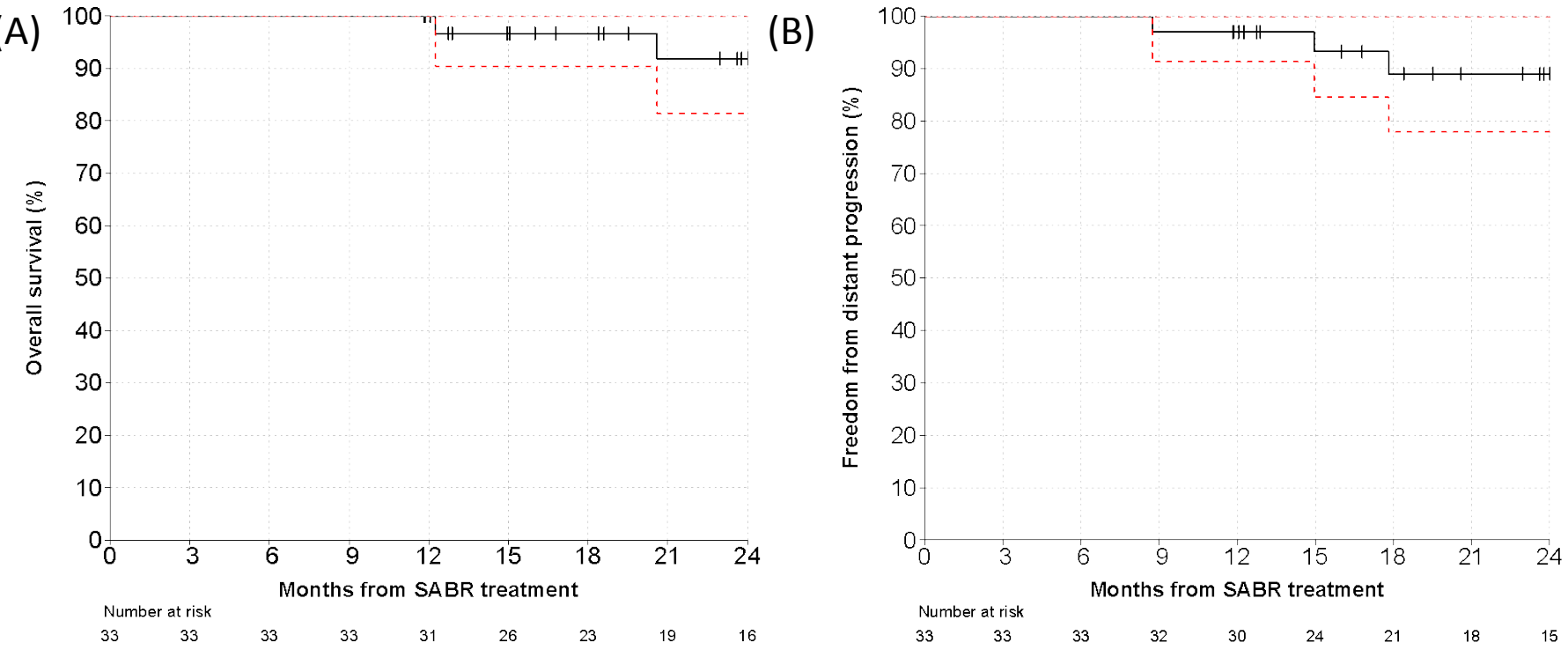

Figure 3

bju_13811_f3.pptx