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Adjuvant management of locally advanced oral squamous cell carcinoma – real world challenges and opportunities

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Adjuvant management of locally advanced oral squamous cell carcinoma – real world challenges and opportunities.

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Abstract

Background: Patients with locally advanced oral squamous cell cancer (LAOSCC) are treated with adjuvant radiotherapy (RT) or chemoradiotherapy (CRT), following surgical ablation. This depends on pathological risk factors and aims to reduce local recurrence risk and improve survival. Delivery of these aggressive treatments is however challenging particularly following major surgery.

Aim: Describe real world delivery of multimodality treatment in LAOSCC, in a UK population with high levels of disease incidence and low socioeconomic status, informing adaptations necessary to deliver gold standard therapy.

Method: Patients with LAOSCC (T1-4 N1-3/T3-4 N0) treated between October 2014–October 2016 with a minimum 24 months follow-up were included. Patients were identified using Somerset Cancer Register and data collected through retrospective case note review. Approval was obtained from relevant NHS institution audit departments and data analysed using IBM SPSS Statistics 24.

Results: Analysis included 129 patients with 82% having initial performance status (PS) of 0-1. The most frequent PS change was 1 point drop (46%). 20 out of 93 patients eligible (22%) underwent

[1] **Abbreviations:**

SCCHN – Squamous Cell Carcinoma of the Head and Neck

CRT/RT – Chemoradiotherapy / Radiotherapy

cK – Cohen's Kappa Statistic

PS – WHO performance status

LA - Locally advanced

OSCC – Oral squamous cell carcinoma

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adjuvant CRT. 40% (37) began adjuvant CRT/RT within 42 days and 85% (79) within 56 days. Delay in initiating adjuvant therapy was associated with higher rates of complication and longer post-operative hospital stay. Concordance between imaging and pathological nodal staging was poor (cK 0.223).

Conclusion: PS frequently declines after complex surgical procedures and long post-operative recovery periods leading to difficulties providing adjuvant treatments within the national guidance of 42 days. Frequent deviation from planned adjuvant therapies highlights the need for improved treatment strategies.

Key Words: Oral cancer, squamous cell carcinoma, chemoradiotherapy, maxillofacial surgery, adjuvant.

Introduction/Background

Treatment strategies for locally advanced oral squamous cell carcinoma (LAOSCC) typically employ multimodality therapy (surgery and adjuvant (chemo) radiotherapy (CRT/RT)) to eradicate primary disease and mitigate the risk of future recurrence. The standard of care for fit patients under 70 years with high-risk disease (extracapsular extension (ECS) in involved nodes and/or involved surgical margins) is cisplatin chemotherapy concurrently with RT [1, 2]. Despite these intensive regimes, long-term survival remains poor [3]. These adjuvant treatment regimes can be highly toxic, and are delivered to a population with multiple comorbidities and frequently, high levels of smoking/alcohol excess. Despite their recommendation within national guidelines, the reality is that delivery of these treatments to patients that have undergone life-changing reconstructive maxillofacial surgery is challenging [4].

Reliable pre-operative staging is extremely valuable when embarking upon complex therapeutic pathways. In order to adequately stage patients before surgical resection imaging (MRI, CT and/or USS) is correlated with physical examination [5]. This unavoidably introduces subjective

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interpretation of findings and inter-observer variability. Maximising the accuracy of pre-operative staging is not only beneficial to patients in improving their journey and providing realistic expectations of their treatment path but also to ensure a streamlined service with early recruitment to clinical trials if available.

Delays to initiating adjuvant RT following radical surgery have a negative impact upon survival [6, 7]. A recent large observational cohort study conducted by Harris et al confirmed the survival advantage of shorter intervals between surgery and adjuvant RT. They reported an improvement in median OS of 4.1 years (95%CI 3.4-4.7) for 25,216 SCCHN patients within their cohort who had an interval of under 42 days compared to those over 50 days [8]. Given these findings, the British Association of Head and Neck Oncologists (BAHNO) and the National Comprehensive Cancer Network (NCCN) advocate initiating adjuvant treatment within 42 days in all sub-sites to minimise the impact of treatment delays upon outcomes and clearly this relies upon a coordinated service [9, 10]. Assessing the deliverability of this target will inform whether the particular complexities of oral and maxillofacial surgery and subsequent recovery periods need to be taken into account in expected treatment times.

We sought to review the current practice within two large tertiary referral Head & Neck units against the recommended adjuvant treatment path outlined within the United Kingdom National Multidisciplinary Guidelines, along with determining the accuracy of pre-operative staging [4]. In parallel, we assessed the frequency with which patients are currently able to complete the course of standard adjuvant therapy and the ability to commence adjuvant treatment within six weeks of surgery (as per BAHNO/NCCN standards) [9, 10].

Objectives and standards

- Concordance of clinical/radiological staging with pathological staging.
- Temporal changes in performance status following surgical ablation/reconstruction and impact upon provision of anticipated “gold standard” adjuvant treatment [4].

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- Proportion of patients suitable for adjuvant CRT compared to those who received CRT and reasons for changing treatment path.
- Proportion of patients who to commenced adjuvant RT within six weeks [9, 10].

Methods

Approval for retrospective data collection and audit was obtained from Aintree University Hospital/The Clatterbridge Cancer Centre and North Manchester General Hospital audit departments. Patients with LAOSCC based on the seventh edition of the American Joint Committee on Cancer Staging (i.e. T1-4 N1-3 or any T3-T4 N0) treated between October 2014 – October 2016 with radical surgery were identified via Somerset Cancer Register [11, 12]. All cases undergoing radical surgery were planned for adjuvant RT/CRT depending on established pathological risk factors. Patient outcomes were obtained through retrospective case note review; of note performance status (PS) was documented at two different time points with evaluations made by different assessors. Detailed tumour resection pathology reports, imaging reports and initial clinical examination documentation were obtained and surgical length of stay with staging information recorded. Surgical complications were graded using the Clavien-Dindo classification system [13]. RT was delivered using Volumetric Modulated Arc Therapy (VMAT) with 66gy in 33 fractions prescribed with concurrent cisplatin either 100 mg/m^2 every 21 days for 3 cycles or 40mg/m^2 weekly. If cisplatin was contraindicated substitution with carboplatin or cetuximab could be considered. The adjuvant RT regimes were 40-65Gy in 20-32 fractions depending on individual treating clinical oncologist preference and pathological risk factors.

Kaplan-Meier survival curves were used to analyse overall survival (OS) and progression free survival (PFS). The Cohen's Kappa statistic (cK) was used as a correlation tool [14].

Results

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A total of 158 patients were initially identified; however 29 patients were subsequently excluded from analysis (primary site other than the oral cavity and/or histological type other than SCC). Of these remaining 129 patients with LAOSCC there were 55 females and 74 males with an average age of 64 years (39-86 years). 53% were current cigarette smokers and 73% current consumers of alcohol (Table 1).

Median OS and DFS for the whole population were 38 months (95%CI 18.8-57.2) and 34 months (95%CI 21.9-46.1) respectively (Figure 1). The three-year OS rate was 44.8% which is in keeping with the three-year OS rate of 45-47% quoted by the NCRAS [3].

A total of 93 (72.1%) patients received post-operative adjuvant treatment. PS was assessed prior to surgical resection and again prior to adjuvant treatment planning. At presentation the majority of patients (72/129, 55.8%) were PS 0 (Table 1). At post-operative assessment only 12 patients were assessed as PS 0 with 89 patients now PS 1 or 2; the most frequent PS drop was 1 point (46%). 8 (6.2%) patients had an improvement in PS following surgical resection; the majority (8) having a rise of 1 point.

Following standard protocols for adjuvant treatment, 93 patients would have been recommended for CRT, (involved margin <1mm and ECS). Of this group, only 20 received CRT; due to deterioration in PS post-surgery (43%), poor PS at first assessment (20%), post-operative complications (8%), early recurrence (7%), comorbidities (3%), previous head and neck RT (3%), patient declined (4%) and no reason documented (13%). Of note there were 30 (33%) aged over 70 years with high risk pathological factors, none of whom received chemotherapy in addition to their adjuvant RT. It was not specified within clinic notes if age was taken into account when deciding whether to offer CRT however it was evident that the majority of these patients had PS≥2 (83%). Of the 20 patients who underwent CRT, all received cisplatin chemotherapy; five were planned to have weekly 40mg/m2 infusions and fifteen 100mg/m2 every 21 days. Six completed the planned course of three cycles of cisplatin chemotherapy. The remaining 14 patients had at least one cycle of treatment omitted due

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to chemotherapy toxicities. Median OS for patients with high risk pathological features were 54 months in those receiving CRT (16.6-91.4), 23 months in those receiving adjuvant RT (95%CI 14.6-31.4) and 9 months in those receiving no adjuvant treatment (95%CI 5.1-12.9) (Figure 2).

73 patients underwent adjuvant RT alone. Despite the recommendation for post-operative RT based on pathological features 36 patients received no adjuvant treatment. Reasons for omitting adjuvant RT were post-operative deterioration in PS (36%), prior head and neck RT (14%), recurrence prior to commencement of RT (8%), patient choice (14%), death prior to treatment (3%), and unknown (25%). Six individuals received palliative RT.

The modal time to commence adjuvant treatment was 42 days (max 116, min 28); 37 patients (40%) began adjuvant CRT/RT within 42 days and 85% (79) began within 56 days. There were 12 patients who took ≥56 days to begin adjuvant treatment and the reasons for this were recovery from post-operative complications (46%), administration error / did not attend when requested (8%), patient moved to different area (8%) and unknown (38%). A delay in initiating adjuvant therapy was associated with longer recovery times and higher complication rate. For those who did not initiate adjuvant therapy within 42 days the median length of hospital stay post-surgery was 16 days along with grade IIIa-V Clavien-Dindo complication rate of 30% (16); compared to 11 days and complication rate of 8% (3) in the group of patients who did meet the 42 day standard (Figure 3).

There was concordance between clinical and pathological tumour staging in 72% of cases (cK 0.551), assessment of nodal staging was less reliable with 49% concordance (cK 0.282). When evaluating radiological tumour staging there was 65% agreement with pathological tumour staging (cK 0.462). Radiological nodal staging showed a 44% concordance with 35% of cases upstaged and 20% down-staged following pathology reporting (cK 0.223). 5 individuals could not be compared as their neck was not included on MRI imaging or they did not undergo neck dissection after imaging (Figure 4).

Discussion

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This research highlights the significant challenges evident in the delivery of "ideal" therapeutic regimes to patients with locally advanced oral cavity cancer. In particular, these results provide evidence of a significant deterioration in patients' PS following surgical treatment for this disease, with 88 individuals (68%) experiencing a demonstrable a fall in PS. The drop in physical fitness is a product of their intensely complex surgical resection and reconstruction and patient co-morbidities. The intimate association and disruption to patients' normal upper aerodigestive tract leads to prolonged recovery times, increased length of hospital stay and the subsequent, increased risk of post-operative complications [15]. Ultimately once patients have recovered from their surgical procedure, any delays within perioperative management bring the patient close to (or even outside) the recommended window for initiating adjuvant treatment. Altered PS and the sequelae of treatment frequently render patients too unwell to consider concurrent cisplatin chemotherapy or RT alone even if they have pathological risk factors which would suggest treatment is indicated.

Only 37 (40%) patients receiving adjuvant treatment did so within the national standard of 42 days. For those treated outside the national standard, 56% (30 patients) were still inpatients at 14 days following their operation (compared to 32%, (12 patients) in those treated within 42 days), and there was a higher rate of grade IIIa-V Clavien-Dindo complications (30% compared to 8%); reinforcing the above conclusions (figure 3). It is evident that this timeline to commencement of adjuvant therapy is not achievable for all patients undergoing surgical procedures for SCCHN and does not take into account the varying surgical complexities across each sub-specialty nor the reality of treating patients with multiple (often undiagnosed) pathologies following a history of long term nicotine and alcohol dependence.

Tri-modality therapy (surgery, chemotherapy and radiotherapy) is an intensive regime which has a dramatic effect upon quality of life [16]. This is reflected in the low proportion of patients completing a full course of adjuvant CRT without modification. Our three year OS rate of 44% reinforces the need for intensification of adjuvant treatments, however the low proportion of patients receiving

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the current 'gold standard' management shows how difficult this will be to achieve in our population. Similarly the TITAN study highlighted patients with LA OSCC as a population difficult to escalate treatment due to advancing age and poor performance status. This study had planned to provide induction cisplatin, 5-fluorouracil and docetaxel chemotherapy prior to ablative surgery for patients with resectable HPV negative SCCHN but could not progress from feasibility to phase III due to difficulties recruiting [16]. Clearly patients with LAOSCC require a nuanced approach to adjuvant treatment with appropriate intensification for those individuals who are fit but also less toxic adjuvant options (namely alternatives to cisplatin chemotherapy) for the majority of patients who have poorer PS and comorbidities. Future clinical trials will consider the integration of new systemic anti-cancer therapies (i.e. immunotherapies) into the neo-adjuvant setting in order to maximise upon the window of opportunity to treat individuals before their physical fitness deteriorates following complex surgical procedures. Clearly careful patient selection and accurate pre-treatment staging is essential to recruit effectively to any study that attempts to enrol at presentation. This research highlights the significant challenges in accurately assessing tumour stage in the preoperative setting by clinical and radiological means alone (concordance between radiological nodal status and definitive pathology was poor (cK 0.223), and hence, the constraints this places on adjuvant treatment planning and will require a recruitment strategy capable of overcoming, or at worst accommodating, the paradox between inaccurate clinic staging and delayed (post-operative) definitive staging.

We recognise some limitations inherent in this survey. The retrospective nature of the data collection meant that there was reliance upon case note documentation; however records were cross-referenced across two NHS trusts to verify data. Review of notes at both surgical and oncology NHS trust sites allowed inter-observer variability in scoring PS and noting treatment toxicities. Despite this, all patients were discussed at multidisciplinary team meetings where PS is reviewed routinely thus minimising this variability. Inclusion of consecutive cases, managed in the respective units, was made in an attempt to mitigate potential selection bias. Assessment of tumour Human

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papillomavirus (HPV) status was not deemed relevant given the low prevalence in oral cavity cancer and, in addition, routine HPV testing is not currently recommended in non-oropharyngeal sites [18, 19, 20].

Conclusions

This study has brought to the forefront the reality of treating patients in the true population with multimodality therapies. Discordance in radiological and pathological staging along with deterioration in performance status as a consequence of treatment intensity necessitates management plans and procedures capable of adaptation to ensure individuals receive the appropriate adjuvant regimes. Future clinical trials should be designed to focus upon the neo-adjuvant treatment window and upon developing alternative, less toxic adjuvant regimes for patients with high risk LAOSCC in order to allow intensification of therapy thus improved outcomes.

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Ethical approval and patient permissions/consent

Local approval was obtained from University Hospital Aintree, The Clatterbridge Cancer Centre NHS Foundation Trust and North Manchester General Hospital to conduct the audit of clinical outcomes. Patient permission N/A

Conflict of Interests

Dr J.J. Sacco has received honoraria from BMS and Immunocore, and has been consulted in an advisory role for Immunocore, BMS, MSD, and Delcath. Dr J.J Sacco has received research funding and/or has held roles as principal investigator / regulatory principal investigator / site principal investigator / member of a steering committee of a study that does not have a principal investigator

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for AZ, BMS, MSD, Immunocore, Replimmune and Amgen. Dr J.J. Sacco has had travel, accommodations, or other expenses paid or reimbursed by BMS, MSD within the last 2 years.

Mr T. Sato, Mr A. Hobkirk, Mr D. Broderick, Ms H. Cashman, Dr H. Wong, Dr A. Haridass, Dr R. Brooker and Mr A.G. Schache certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Dr R. Brooker and Mr A.G. Schache are not directly receiving funding from BMS however they are currently contributing to the set up and opening of the NICO trial which is being funded by BMS.

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Table 1: Patient and treatment characteristics

PATIENT CHARACTERISTICS	FREQUENCY	PERCENT	MEAN	MIN/MAX
Age				
<50	13	10.1	64	39-86
51-60	32	24.8		
61-70	42	32.6		
71-80	32	24.8		
>81	10	7.8		
Male	74	57.4		
Female	55	42.6		
Non Smoker	34	26.4		
Ex-Smoker	25	19.4		
Current Smoker	69	53.5		
Unknown	1	0.8		
Nil Alcohol	32	24.8		
Current Alcohol	95	73.6		
Unknown alcohol	2	1.6		
PS at initial assessment				
PS 0	72	55.8		
PS 1	34	26.4		
PS 2	14	10.9		
PS 3	7	5.4		
PS 4	1	0.8		
Unknown	1	0.8		
PS at adjuvant assessment				
PS 0	12	9.3		
PS 1	46	35.6		
PS 2	43	33.3		
PS 3	16	12.4		
PS 4	1	0.8		
PS 5	1	0.8		
Unknown	10	7.8.0		
Time to RT/CRT				
20-35 days	16	17.2		
36-42 days	21	22.6	47.4	25-116
43-49 days	26	28.0	days	days
50-56 days	16	17.2		
≥57 days	12	12.9		
Unknown	2	2.2		
Adjuvant treatment				
Chemoradiotherapy	20	15.5		
Radiotherapy	73	55.8		
None	36	28.7		

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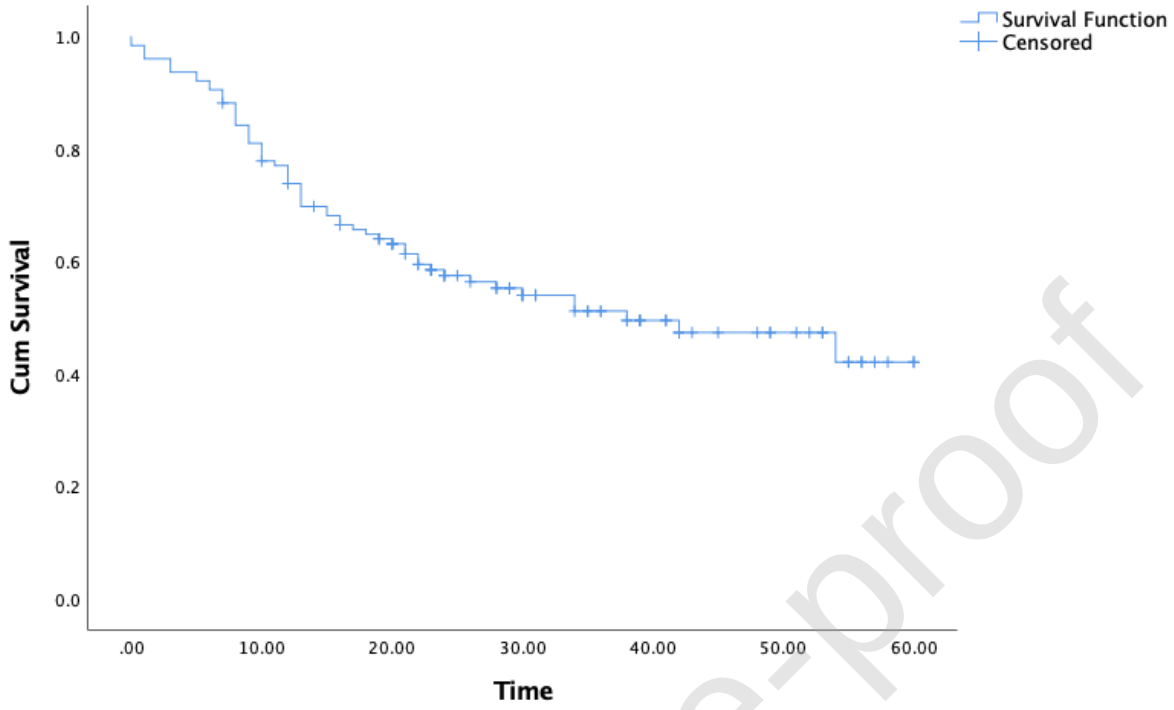
Figure 1: Overall Survival Kaplan-Meier – whole population.



Means and Medians for Survival Time

Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
36.316	2.199	32.007	40.626	38.000	9.795	18.802	57.198

a. Estimation is limited to the largest survival time if it is censored.

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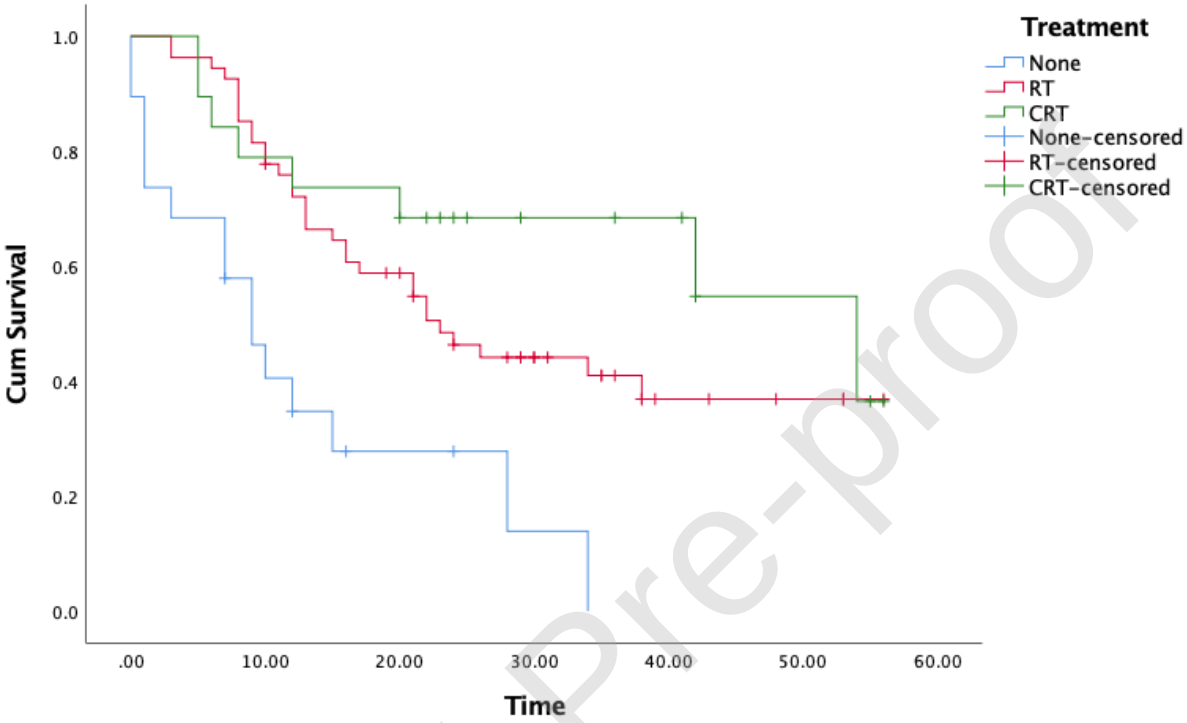
Figure 2: Overall Survival Kaplan-Meier – Patients with high risk pathological features



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Means and Medians for Survival Time

Treatment	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
None	13.025	2.984	7.176	18.874	9.000	2.012	5.056	12.944
RT	30.885	2.933	25.137	36.633	23.000	4.274	14.623	31.377
CRT	38.982	4.958	29.265	48.700	54.000	19.074	16.615	91.385
Overall	29.128	2.338	24.545	33.711	22.000	4.948	12.301	31.699

Figure 3: Reducing number of inpatients per week interval after radical surgery

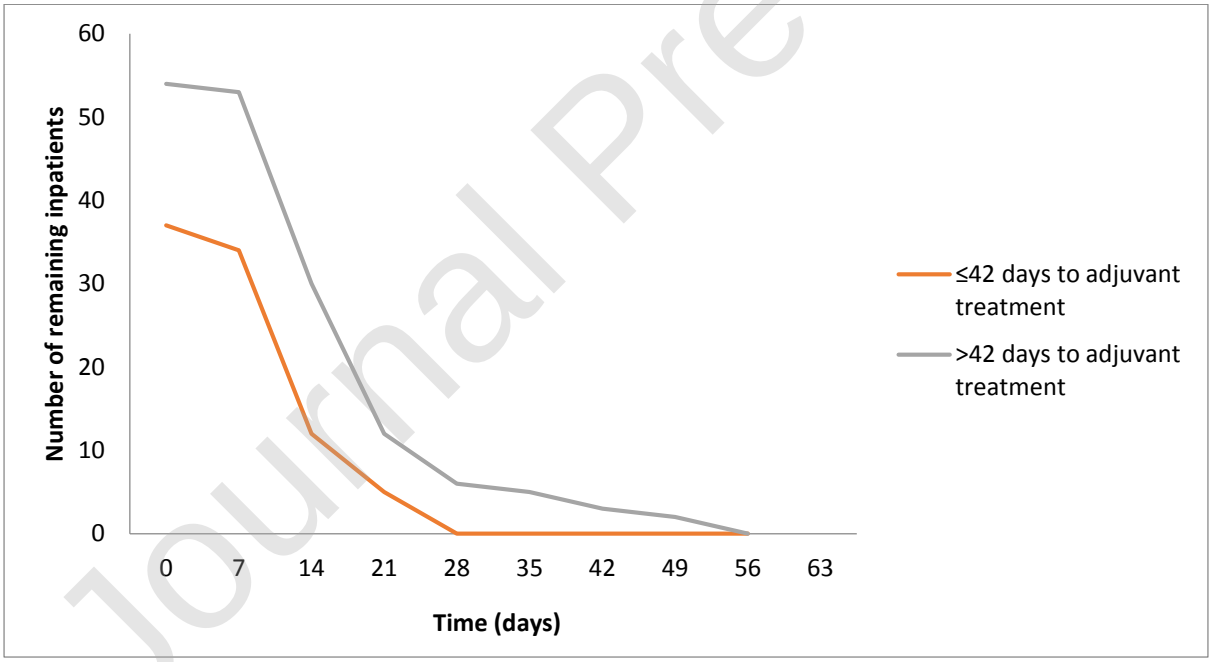

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Table 2: Tumour characteristics

TUMOUR CHARACTERISTICS	FREQUENCY	PERCENTAGE
Margin		
Involved (<1mm)	56	43.4
1-5mm	49	38.0
>5mm	24	18.6
Nodal ECS		
ECS +	58	45.0
ECS -	68	52.7
Not assessed	3	2.3
Clinical Staging		
T1	6	6.7
T2	41	31.5
T3	8	6.7
T4	74	55
N0	84	65.1
N1	22	17.1
N2a	3	2.3
N2b	12	9.3
N2c	6	4.7
Nx	2	1.6
Radiological Staging		
T1	8	6.2
T2	22	17.1
T3	11	8.5
T4	75	58.1
Not assessed	3	2.3
N0	62	48.1
N1	22	17.1
N2a	1	0.8
N2b	27	20.9
N2c	10	7.8
Nx	7	5.4
Pathological Staging		
T1	6	4.7
T2	38	29.5
T3	24	18.6
T4	61	47.3
N0	39	30.2
N1	39	30.2
N2a	0	0
N2b	36	27.9
N2c	11	8.5
Nx	4	3.1

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Figure 4: Concordance between pathological and radiological staging

Radiological T stage (Tr)	Pathological T stage (Tp)				
	1	**2**	**3**	**4**	**Total**
1	**1**	4	2	2	9
2	5	**21**	4	2	32
3	0	5	**6**	0	11
4	0	8	11	**57**	76
X	0	0	1	0	1
Total	**6**	**38**	**24**	**61**	**129**

Tr vs Tp	N	%
Pathologically downstaged	30	23%
Same	85	65%
Pathologically upstaged	14	11%
Total	**129**	**100.0%**

Tr vs Tp	Value	Asympt. Stand. Error[a]	Approx. T[b]	Approx. Significance
Measure of Agreement: Kappa	0.462	0.057	7.923	.000
N Valid Cases	129			

Radiological N stage (Nr)	Pathological N stage (Np)					
	0	**1**	**2a**	**2b**	**2c**	**Total**
0	**29**	14	1	14	5	63
1	3	**10**	0	7	2	22
2a	0	0	**0**	1	0	1
2b	5	10	0	**12**	0	27
2c	2	4	0	1	**4**	11
Total	**39**	**38**	**1**	**35**	**11**	**124**

Nr vs Np	N	%
Pathologically downstaged	25	20%
Same	55	44%
Pathologically upstaged	44	35%
Total	**124**	**100.0%**

NB Unable to compare results in 5 patients

Journal Pre-proof

Journal Pre-proof

Nr vs Np	Value	Asympt. Stand. Error[a]	Approx. T[b]	Approx. Significance
Measure of Agreement: Kappa	0.223	0.058	4.270	.000
N Valid Cases	124			

Journal Pre-proof