Journal of Radiotherapy in Practice

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Using data extracted from a radiotherapy record & verify system to infer outcomes of patients treated for radical brain cancer

Martin Sykes

Radiotherapy, Hull University Teaching Hospitals NHS Trust, Castle Road, Cottingham, East Riding of Yorkshire, England

Original Article

Cite this article: Sykes M. (2020) Using data extracted from a radiotherapy record & verify system to infer outcomes of patients treated for radical brain cancer. *Journal of Radiotherapy in Practice* **19**: 4–9. doi: 10.1017/S1460396919000359

Received: 27 February 2019
Revised: 15 April 2019
Accepted: 16 April 2019
First published online: 24 May 2019

Key words:
Glioblastoma; informatics; outcomes; radiotherapy; survival

Address for correspondence:
Martin Sykes, Radiotherapy, Queens Centre, Castle Hill Hospital, Cottingham, HU16 5JQ, UK.
Tel: 01482 461216. E-mail:
martin.sykes@hey.nhs.uk

Abstract

Aim: The aims of this study were to explore the outcome measures that can be recorded in a radiotherapy IT system and the extract mortality results for a group of patients receiving radical radiotherapy treatment for primary brain cancer.
Method: Treatment mortality outcomes were extracted from a radiotherapy database and were compared to treatment technique used between 1 January 2011 and 31 December 2017. The patients selected received 1 course of radiotherapy of 60 Gray in 30 treatments ($n = 270$). These patients received either Conformal Radiotherapy (CRT) ($n = 127$) or Volumetric Modulated Arc Therapy (VMAT) ($n = 143$). Kaplan–Meier plots were generated for these two groups to assess the survival. The median survival was 20·1 months (95%CI = 16·8 −23·4) and 14·0 months (95%CI = 11·1−16·5) for CRT and VMAT, respectively.
Discussion: Surprisingly, the results of this data extraction demonstrated that CRT gave better survival for this group of patients, than VMAT. The reason for the difference in survival is unclear and more data are needed to explain the result.
Conclusion: This demonstrates that not only that a radiotherapy database can be used to extract outcome measures but that it must be done to explore where a change in treatment delivery has been of benefit to the patients or not.

Introduction

Brain cancers account for 3% of all new cancer diagnoses per year in the United Kingdom with 11,423 new cases diagnosed in 2015 alone; the most common type being Astrocytoma, accounting for 34% of all brain tumours.[1] The most common form of astrocytoma and the most aggressive is Grade IV, sometimes called Glioblastoma Multiforme (GBM). The standard treatment for both grade III and grade IV astrocytoma is surgical debulking followed by a course of radiotherapy; 60 Gray in 30 equal fractions with concurrent & adjuvant Temozolomide.[2] The overall survival for patients diagnosed with GBM is poor; the median survival for 1, 2 and 5 years was 28·4, 11·5 and 3·4%, respectively, in England between 2007 and 11.[2]

Within radiotherapy, the term 'improvement' usually translates as a better conformity of the dose to the target and greater avoidance of other structures.[3] The use of conformal treatment (CRT) plans using static beams aimed at the tumour volume from different angles has been generally replaced by the use of Intensity Modulated Radiotherapy (IMRT), specifically an evolution of IMRT called Volumetric Modulated Arc Therapy (VMAT). Comparisons between CRT and IMRT for the treatment of radical cancer have been carried out examining different aspects of radiotherapy treatment plans. It has been suggested that VMAT offers greater dose conformity around the tumour volume while being able to deliver the treatment in a shorter time[4] and that where the tumour is close to organs at risk, IMRT can deliver the prescribed dose and spare these structures with greater effectiveness than CRT.[5,6] Furthermore, it is commonly assumed that the advantage gained by using VMAT or IMRT improves survival and Quality of Life.[6] However, this assumption is seldom evidenced by correlation of use of IMRT/VMAT with improvements in Patient Reported Outcome Measures (PROMs).

CRT poses significant challenges of delivering radiotherapy to the brain, especially where the tumour is close or overlapping with organs at risk. A compromise must be met, either on the dose delivered to the tumour volume or the dose to the organ at risk. The advantage with VMAT is that this compromise is not needed as much, as the dose can be delivered to the tumour without overdosing the sensitive structures.[6] It would therefore be a reasonable assumption that VMAT can deliver the 60Gy to the tumour needed to improve patient outcomes while minimising the damage to normal tissues, (i.e., so the patient's overall survival and quality of life may be increased).

The aim of this study was to compare the Overall Survival (OS) of patients treated with radical CRT and VMAT for Astrocytoma, using 60 Gray in 30 fractions. This study was

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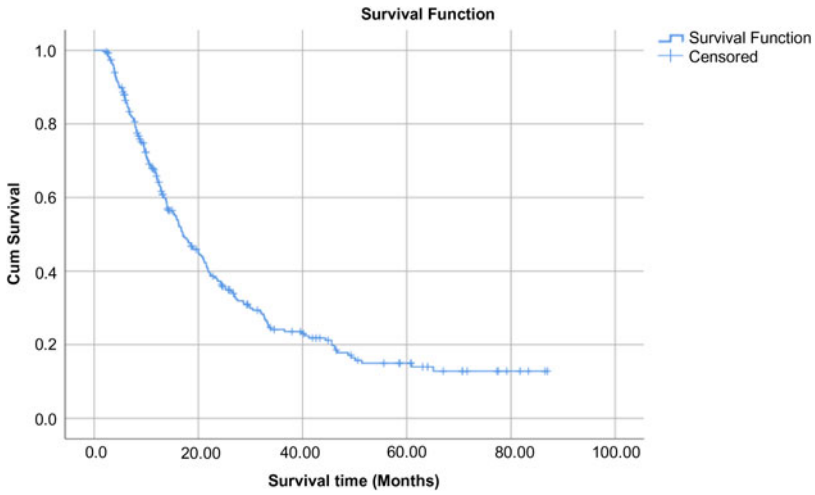

Figure 1. Kaplan-Meier plot for Overall Survival.

performed at a single UK Radiotherapy centre by extracting the data already contained within the radiotherapy department's Record & Verify database in this case, the ARIA database, created by Varian Medical Systems (Crawley, UK).

Method

The ARIA database was mined for data using a Microsoft Access reporting tool and all patients with an ICD10 diagnosis code of C71 that were treated between 1 January 2011 and 31 December 2017 were transferred to an offline Microsoft Excel Spreadsheet. Consent for this process was not required as this was covered by a hospital agreement for secondary use of patient information. This report contained basic patient demographics (Unique Patient ID numbers, date of Birth) and the date of referral for treatment, along with the date of death if the patient had died. The ICD10 diagnosis codes are an International Classification of Diseases table, created by the World Health Organization that codes each disease type, with a code of C71 relating to astrocytoma disease only.[7]

All data were interrogated by an in-house Physics Eclipse (Varian. Crawley, UK) API script that returned treatment information about each patient, including the total treatment dose received, the number of fractions and the treatment delivery technique used.

The original list included all patients with a C71 diagnosis code, regardless of the treatment used, so the list was further filtered to only include only those patients that had the standard of care 60 Gray in 30 fractions. Any patients who received treatment for recurrent disease were removed, and the patients' age at referral was calculated manually.

Survival in terms of years was compared with patients who received CRT and patients who received VMAT, the null hypothesis would be that there is no difference in survival between those patients who received CRT and those who had VMAT.

Kaplan–Meier survival curves were plotted with the filtered data, all patients who were still alive and so had no date of death entered in their record, had the date of data capture entered into the date of death field so these could be censored correctly when the Kaplan–Meier survival curves were calculated. The Kaplan–Meier plots 'censor' all data points where the event of interest has not happened, in this case where the patient has survived beyond the date where the data were captured. Furthermore, a table was then produced to demonstrate median survival, and 95% Confidence Interval will indicate the accuracy of the data after censoring; a smaller interval will indicate a more accurate result.[8]

An independent samples t-test was also conducted to compare the mean survival between patients receiving CRT and VMAT to provide further statistical significance to the results. A Cohen's d test was also applied to this result to assess the magnitude of the impact.

A Chi-squared test was also carried out to ascertain if there was any difference between the age at referral and the treatment technique. The null hypothesis for this test would be that there is no significant difference between the ages and the technique delivered.

All data analysis was carried out using the statistical software, SPSS v25.

Results

The report generated included all patients treated with radiotherapy for brain cancer with an ICD10 code of C71, with a radical dose of 60 Gray delivered in 30 equal fractions over six weeks between January 2011 and December 2017 at Hull and East Yorkshire NHS Trust ($n = 270$). At the time of sampling 72·2% ($n = 195$) had died. The age at referral ranged from 22·2 to 75 years with a mean age at referral of 57·1 years. The survival time in months had a range of 1·9–87 months with an overall median survival of 13·97 months.

A Kaplan–Meier overall survival plot for the whole population (Figure 1) was produced alongside a survival plot comparing those patients who had Conformal Radiotherapy CRT and those who had Volumetric Modulated Arc Therapy (VMAT) (Figure 2).

The estimated median overall survival from the Kaplan–Meier plots was calculated at 17·0 months (95% CI = 14·2–19·9). The estimated median survival for those patients who received CRT was 20·1 months (95% CI = 16·8–23·4) and the estimated median survival for VMAT patients was 14·0 months (95% CI = 11·1–16·8), which is a difference of 6·1 months. The mean and median survival is presented in Table 1.

An independent sample t-test was conducted to compare the survival time in months between patients receiving CRT or VMAT for radical treatment of brain cancer. There is a significant difference between the two groups, $t(268) = 6{\cdot}401$, $p < 0{\cdot}001$, with CRT patients (M = 27·93, SD = 22·21) surviving longer than VMAT patients (M = 14·51, SD = 10·98). The magnitude of the

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Table 1. Mean & Median survival time

Means and Medians for survival time								
	Mean[a]				Median			
			95% confidence interval				95% confidence interval	
Treatment	Estimate	Std. error	Lower bound	Upper bound	Estimate	Std. error	Lower bound	Upper bound
CRT	30·551	2·404	25·838	35·263	20·088	1·681	16·792	23·383
VMAT	20·376	1·502	17·431	23·320	13·973	1·468	11·096	16·849
Overall	27·816	1·812	24·265	31·368	17·030	1·468	14·153	19·907

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

Table 2. *t*-Test comparing survival in months and choice of treatment technique

Independent samples test										
		Levene's test for equality of variances		t-test for equality of means						
									95% confidence interval of the difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	Lower	Upper
Survival time (Months)	Equal variances assumed	58·691	0·000	6·401	268	0·000	13·42653	2·09757	9·29672	17·55633
	Equal variances not assumed			6·174	179·161	0·000	13·42653	2·17474	9·13513	17·71793

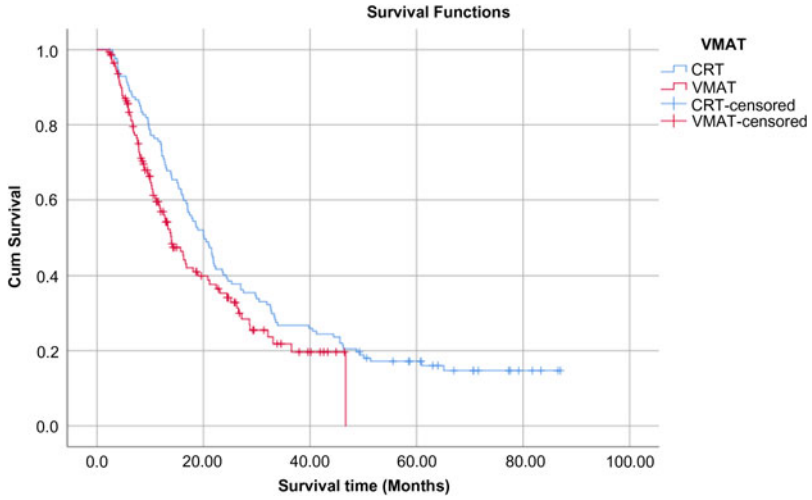

Figure 2. Kaplan-Meier plot comparing CRT vs VMAT.

differences in the means (mean difference = 14·43, 95% CI: 9·14–17·72) was large (Cohen's $d = 0·766$) (Table 2).

A further independent sample t-test was carried out to compare the age in years at referral and the treatment technique used. There is no significant difference between the two groups, $t(268) = -0·436$, $p > 0·5$ with an age at referral for CRT patients = 56·8 years (SD = 11·6) and VMAT patients = 57·4 years (SD = 11·2) (Table 3).

To further demonstrate this, a Chi-Squared test was carried out comparing the treatment technique and the age of the patients. The patients were split into two age categories; above or below the median age (60·2 years) (Table 4).

The Chi-Squared value was low (0·134, $p > 0·5$) which would suggest that the null hypothesis cannot be rejected so that there is no significant difference between the ages and the technique delivered.

Discussion

The null hypothesis for the treatment technique would assume that there would be no difference in the overall survival between those patients who received CRT and those who received IMRT/VMAT. As the results demonstrate, this null hypothesis has been rejected

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Table 3. t-Test comparing age of patient at referral with choice of treatment technique

Independent samples test										
		Levene's test for equality of variances		t-test for equality of means						
									95% confidence interval of the difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	Lower	Upper
Age at referral	Equal variances assumed	0·182	0·670	−0·436	268	0·663	−0·6073	1·3919	−3·3478	2·1331
	Equal variances not assumed			−0·435	261·805	0·664	−0·6073	1·3948	−3·3537	2·1391

Table 4. Chi-Squared cross tabulation comparing age at referral with treatment technique used

Median Age * Technique cross tabulation				
Count				
		Technique		
		ARC	STATIC	Total
Median Age	Below median	70	65	135
	Above median	73	62	135
Total		143	127	270

	Value	df	Asymptotic significance (2-sided)
Pearson Chi-Square	0·134[a]	1	0·715
Continuity correction[b]	0·059	1	0·807
Likelihood ratio	0·134	1	0·715
N of valid cases	270		

[a] 0 cells (0·0%) have expected count less than 5
[b] Computed only for a 2 × 2 table

and there is a statistically significant difference in the OS of these two groups. The median OS for CRT and VMAT was 20·9 months (95% CI = 16·8–23·4) and 14·0 months (95% CI = 11·1–16·9), respectively.

As discussed, 'radiotherapy improvement' usually refers to technological advances that result in better dose conformity around the target volume and avoidance of other structures.[3] Although these advances are always welcome and in theory improve patient outcome, there is little in the literature that substantiates this by actually examining patient outcomes.[6] The results from this study suggest that for patients treated with 60Gray in 30 equal fractions for Astrocytoma using CRT, the median overall survival rate is worse for those patients with an 'improved' treatment technique (VMAT) by a significant factor of 6·9 months.

When the data are examined using an independent samples t-test the results are equally compelling. The mean survival difference was $t(268) = 6{\cdot}4$ months ($p < 0{\cdot}001$). The magnitude of this result, (measured using Cohen's $d = 0{\cdot}766$) would indicate that this result was not only statistically significant but also affects 76·6% of the population. As increasing age relates to poorer survival in patients with astrocytoma[9] the second *t*-test examined the relationship between patients age at referral and the treatment technique used. This *t*-test demonstrated that there is no significant difference in age between the two groups of patients, the mean difference is $t(268) = 0{\cdot}44$ years ($p > 0{\cdot}5$). The Chi-Squared test also confirmed this result, with a low probability (Chi-Square = 0·134, $p > 0{\cdot}5$), which accepts the null hypothesis that there is no statistically significant difference between the age of the patient and the technique used. Therefore, any difference in OS between the two treatment modalities cannot be attributed to a difference in age at referral.

When the Kaplan–Meier curves are examined (Figure 2) there is a clear difference between the two groups, however, the curves would appear to start to meet for the 20% of patients that survive the longest. More time is needed to assess if this is the case or if the VMAT survival continues to decline below the CRT rate.

The results presented here are not what would be expected,[5] so the reasons for the poorer OS associated with a more advanced technique needs to be examined further. The data presented have age associated with each patient, and has already been explained, this cannot explain the difference in the OS between the groups. More data are required to add some context to these results, but these data are not available at this time.

Another limitation of this data is the cause of death is not known. The date of death is recorded; however a cause of death is not recorded, so it is assumed that death has been caused, in part at least, by the brain tumour or the treatment.

Additional information that would be of assistance in making any decisions regarding choice of treatment modality are items such as the performance status at referral such as the Eastern Cooperative Oncology Group (ECOG) scale.[10] Without knowing the performance status of each of the patients involved in this study limits the ability to make any conclusions regarding the effectiveness of each treatment modality. The performance status can be affected by the size and location of the tumour, as well as the effect that the surgery had on the patient. It would not be an unreasonable proposition to suggest that for a patient with a larger tumour next to a sensitive structure (such as the brain stem) would have a poorer performance status after surgery than a patient with a smaller tumour located further away from sensitive structures. In such an example, delivering 60Gray in 30 equal fractions with CRT may not have been considered due to the high dose that the brain stem would have received and the side effects that this would have caused the patient. In such a case, a lower dose of radiotherapy may have been utilised to try and slow the tumour growth, rather than to attempt a cure. However, with VMAT, the dose can be conformed to the tumour site with greater accuracy, so treating this theoretical patient to 60Gy would be considered more readily. This is why knowing the performance status of the patient prior to treatment is so important.

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The dose that the patient receives to the tumour site has a direct relationship to the patient's survival, and a dose of 60Gray in 30 equal fractions is the standard of care, and the dose that should be given, where possible. However, the dose received by other organs also needs to be considered. The tolerance dose of the cochlea is 45Gy, the optic chiasm tolerance dose is 55Gy and the brain stem is 55Gy.[11] Where the tumour site is close to any of these structures, a clinical decision needs to be made to either irradiate all of the tumour volume to the prescribed dose and potentially overdose these sensitive structures or compromise the dose to the tumour to save these structures. Over-irradiation of the brain stem may obtain tumour control, but it could also cause irreparable damage to the brain stem, potentially shortening the patient's survival, so compromising the tumour dose may be the preferred option. An overdose to the optic chiasm can cause blindness, in which case it may be prudent to ask the patient what their preferred option may be; higher chance of tumour cure and loss of sight or save the patients vision and accept that a cure is highly unlikely.

Within any radiotherapy planning system, the doses to the tumour and the organs at risk are recorded. As these are 3D volumes, the doses can be measured as a minimum, maximum and mean dose. As this information is stored within the database, it could also be extracted and analysed in the same way as has been conducted for this study, albeit with a lot more work within the API Scripting models. This data, has been stored within the databases for many years, but is only now available for such large-scale data extraction techniques, so being able to compare survival against the large variety of dose information available has not yet been done, but it is at least now possible.

The tolerance doses that are referred to by radiotherapy departments are based on recommendations from the Royal College of Radiologists (RCR)[12] which in turn use published literature that has been peer reviewed and subjected to systematic review. Many of the tolerance data information is derived from the QUANTEC study which uses published data and derived information to make suggestions for the tolerances recommended.[11] This study has many caveats and makes many assumptions that the authors freely acknowledge, however, without any other information available, this is the primary source for tolerance doses. All of the data is based upon CRT treatment, but many of the tolerance levels have been applied by the RCR to VMAT treatment, where information about chronic side effects is unavailable, such as for GBM patients, other patient groups with different diseases are used whose prognosis is better such as low-grade glioma patients.

If large volumes of dose data can be extracted from planning systems and compared to survival and quality of life information, then departments can start to derive their own tolerance levels, based on the patients that they have treated, and will be 'real' data, not information from studies that they didn't participate in using techniques and equipment that they do not use.

The Clinical Target Volume (CTV)–Planning Target Volume (PTV) margin is derived from local data analysing the daily setup errors seen on the treatment machines, as well as published data and national recommendations; a 3–5mm expansion is not considered unreasonable.[13] These margins were true for CRT and were transferred to VMAT treatment; however, the volume receiving 90% of the dose (54Gy) would have been greater for CRT than for VMAT, due to the higher conformity of VMAT treatment. It may be that transferring the same CTV–PTV margin from CRT to VMAT was inappropriate and that a larger margin should have been applied. However, this assumption cannot be proven as there is insufficient evidence in this study to provide any proof, but it does ask a serious question of the radiotherapy community as to whether it was appropriate to apply the same tolerance doses and PTV margins from CRT to VMAT treatment.

In addition; as more patients are surviving cancer, having PROMs recorded routinely by radiotherapy centres would provide much more detailed information about a patient's condition and how well they are surviving from their treatment.

Conclusion

This study has demonstrated that it is possible to extract outcome data for patients who have received radiotherapy by using the radiotherapy record and verify IT systems. Not only is it possible but it is also advantageous as it provides the ability to relate outcome data to treatment plan and dose information. The results from the data extraction were surprising as it showed that the more advanced treatment technique actually had poorer survival rates than the more basic treatment. The reasons for this are unknown and have demonstrated that more data about radiotherapy patients is required to provide context to the only outcome statistic currently recorded: survival.

Author ORCIDs. Martin Sykes, 0000-0002-2614-1712

Acknowledgements. This study was part of the final submission for an MSc dissertation in Health Informatics at University of Sheffield. Thanks must therefore be given to Prof. Peter Willets at the University of Sheffield for his support during the writing of this dissertation.

Financial Support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflicts of Interest. None

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