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Research Article

Adjuvant Treatment of Grade 4 Glioma, Outcomes at a UK Tertiary Center

Louise Price*, Charlotte Ziff, Abdelfattah Elmasry and Selvaraj Giridharan

The Cancer Centre, University Hospital North Midlands (UHNM), Stoke-on-Trent, United Kingdom

***Corresponding Author:** Louise Price, The Cancer Centre, University Hospital North Midlands (UHNM), Stoke-on-Trent, United Kingdom.

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Abstract

The 5-year overall survival (OS) for Glioblastoma (GBM) remains low. The cohort had a lower percentage of completing adjuvant treatment than those reported in trials. Therefore unplanned 6 cycles of adjuvant treatment and the effect on survival outcomes were assessed. Survival data for patients with Gliadel wafer insertion at the time of primary surgery was also assessed. The combination of these factors on survival outcomes was also assessed.

Methods: The retrospective cohort study of 110 patients who underwent neurosurgery followed by chemoradiotherapy (CRT) 60 Gray in 30 fractions and adjuvant Temozolomide (TMZ) was carried out from 2007 to 2016. Overall survival (OS) and progression-free survival (PFS) were assessed and a number of subset analyses were carried out.

Results: The period of OS was 16 months and PFS was 11.9 months. 57% of patients completed 4-6 cycles of adjuvant TMZ 43% received 3 or fewer cycles of TMZ. Those unable to complete planned adjuvant TMZ had a poorer OS (10 vs 20 months, Cox analysis P-value 0.0003).

For patients having maximal safe debulking plus Gliadel wafer insertion, median OS was improved, 19.5 months P=0.06. In the group with the combination of significant factors, the median OS was 2 months greater than those that did not receive Gliadel wafers and could not complete 4 cycles of adjuvant TMZ.

Conclusion: Survival outcomes were improved with Gliadel wafer insertion and completing 4-6 cycles of TMZ. Consequently, the combination of these factors led to improved outcomes.

Keywords: Glioblastoma; Gliadel wafers; Overall survival.

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Background

Glioblastoma (GBM) or grade 4 Glioma, is the most common primary central nervous system tumor. The incidence in England is 4.64 per 100,000 per year from 2005-2011 [1] and is the leading cause of cancer-related deaths in those under 40 years. Primary surgical management of glioblastoma is maximal safe debulking surgery, which is defined as more than 90% of the tumor removed at the time of surgery, this has been shown to significantly improve survival [2].

Where this is not possible this is termed partial debulking. Carmustine implants (Gliadel wafers) have been approved for insertion along the operative bed where maximal safe debulking has taken place [3].

A meta-analysis of 513 patients demonstrated a survival advantage after Gliadel wafer insertion [4]. However, the use of Gliadel wafers varies within different neuro-surgical centers. Therefore, the effects of Gliadel wafer insertion in the center were investigated. The standard of care for first-line management is maximum safe debulking followed by radiotherapy to a dose of 60Gy in 30 fractions with concurrent Temazolamide (TMZ) 75mg per meter squared and 6 cycles of adjuvant TMZ at 200mg per meter squared as per Stupp, et al. [5]. Within this trial median progression-free survival (PFS) was 6.9 months and the median overall survival (OS) was 14.6 months. A minority, 9.8%, survived 5 years and beyond [5-6].

Within the first line sets the use of both vascular growth factor inhibitors (Bevazuimab) [7] and MTOR inhibitors Everolimus [8] have been trialed alongside chemoradiotherapy showing no significant effect on OS or PFS. Tumor treating fields (TTF) device use has shown some additional improvement in survival in those patients who do not have contraindications [9]. Its use is not approved by NICE NG99 [10-11].

In spite of these incremental improvements, median survival still remains poor, ranging between 14 and 21 months, especially in the MGMT unmethylated group. MGMT methylation is a predictive biomarker of response to TMZ [12] regardless of standard treatment is 6 cycles TMZ. More than 6 cycles of adjuvant TMZ have been investigated, without statistically significant improvement in PFS or OS [13]. A meta-analysis confirmed extended maintenance TMZ beyond 6 cycles did not improve overall survival [14].

There are no studies, investigating the effects of stopping TMZ early due to clinical complications before completing 6 cycles of adjuvant TMZ.

Aim

In this retrospective review, the tertiary neuro-surgical center experience in the management of glioblastoma was investigated. Several outcome measures influencing overall survival and progression-free survival in relationship to Gliadel wafer insertion, the number of adjuvant chemotherapy cycles completed, redo debulking surgery on relapse the usage of second-line chemotherapy was observed. The impact of both Gliadel wafer insertion and completing adjuvant TMZ on OS and PFS were also reviewed.

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Methods

Data were collected from 110 patients retrospectively, who were diagnosed with grade 4 Glioma (WHO2016CNS classification), who had completed standard treatment of surgery followed by adjuvant chemoradiotherapy, 60 Gray in 30 fractions, and who had at least one cycle of adjuvant TMZ chemotherapy. To allow for 5 years of patient follow-up, data were collected 5 years prior to the point of data collection.

Data was collected from that undergoing neurosurgery from 2007 to December 2016, and included known prognostic factors; age, WHO performance status, and presence of maximal debulking (defined as 90% or more of visible tumor excised at the time of surgery). The treatment parameters, Gliadel wafer insertion, and completion of chemo-radiotherapy were observed. Data were reviewed from clinical surgical and oncology records. PFS and OS were taken from the date of surgery. Progression of disease was taken from Multi-disciplinary team meeting outcomes in which experts reviewed clinical and radiological evidence. R-software V4.0.0 statistical package was used to carry out median, standard deviation, cox regression, or Log-rank analysis. All methods were performed in accordance with the relevant guidelines and regulations. This retrospective cohort review has not been approved by a local ethics review committee, as data were retrospectively collected from existing clinical records by members of the clinical team. Stored on password-encrypted NHS devices. Data were not collected prospectively and therefore this retrospective review in no way affected decision-making and patient care.

Results

Within the cohort of 110 patients the median age was 60 years (see Table 1) with a PFS of 12 months and with 95% Confidence interval (CI) of 9.5–13.7 months (See Figure 1). The median OS is 16 months (95% CI 15–20 months) (See Figure 2). The 5-year survival rate is 7%.

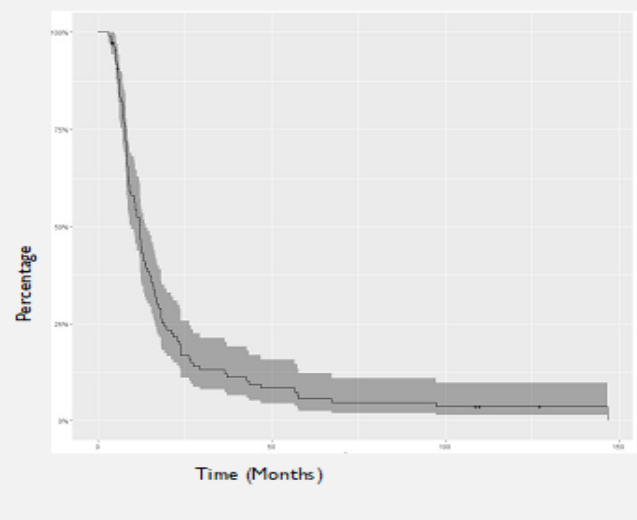

Figure 1: Kaplan–Meier plot to show PFS for GBM at UHNM.

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Characteristic	Raw numbers (n) and percentages
Median age	60 years (range 17–79 years)
Median time from diagnosis to start of radiotherapy	71 days (range 21 –168 days)
Performance status	
PS 0	33 (30%)
PS 1	73 (67%)
PS >/= 2	4 (3.6%)
Neurosurgery	
Maximal debulking	39 (35.4%)
Partially de-bulked	46 (41.8%)
Biopsy only	25 (22.7%)
Adjuvant Chemo-radiotherapy	
CRT plus completed 6 cycles of TMZ	63 (57.3%)
Gliadel wafer insertion following maximal debulking surgery	
Yes	24 (21.8%)
No	86 (78.2%)
Unable to collect data on Molecular parameters as data collected from 2007 onwards	

Table 1: Baseline statistics of UHNM cohort N=110.

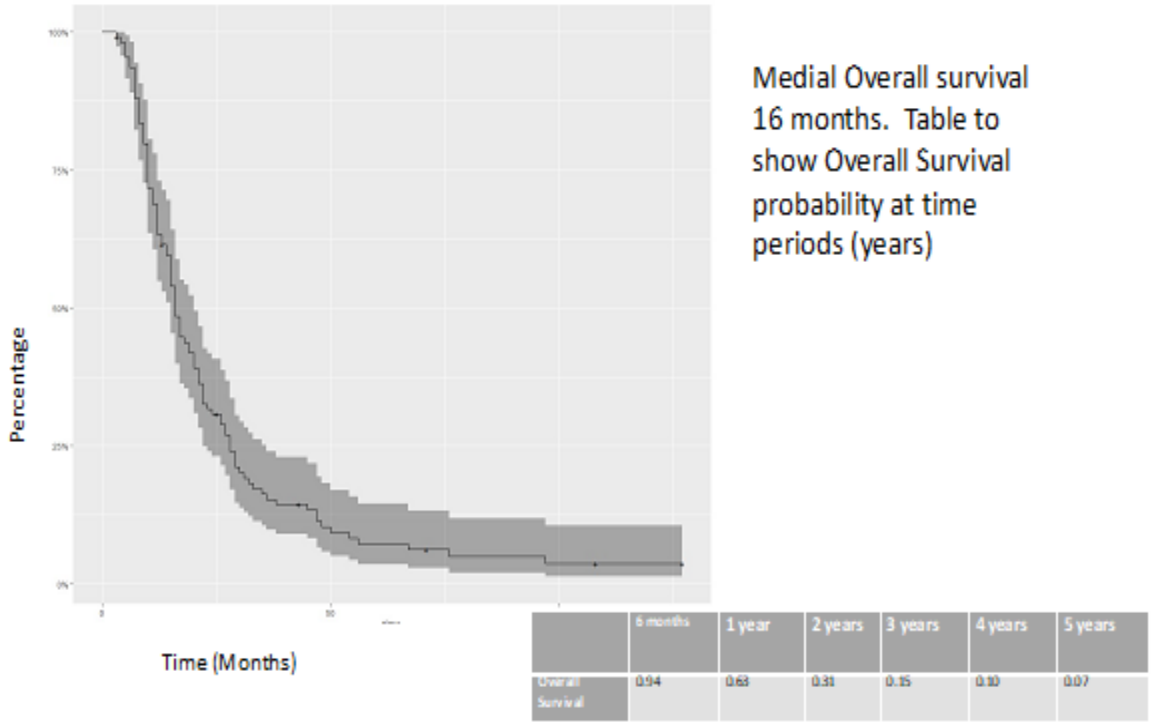

Figure 2: Kaplan–Meier plot to show overall survival for GBM at UHNM.

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Maximal debulking was achieved in 35.5% (n= 39), partial debulking in 41.8% (n=46) and 22.7% (n=25) had biopsy only. In the cohort, maximal debulking surgery alone was not a predictor of OS (Maximal debulking P-value 0.38).

Patients who had maximal safe debulking and were eligible for Gliadel wafer insertion (n = 24) had an improved median OS of 19.5 months (95% confidence interval 14-30).

For those with Maximal, safe debulking without wafers median OS was 16 months (95% confidence interval 14 – 21), P=0.06 (See Figure 3). On Cox regression analysis Gliadel wafer insertion was a statistically significant predictor of overall survival, P-Value, 0.008.

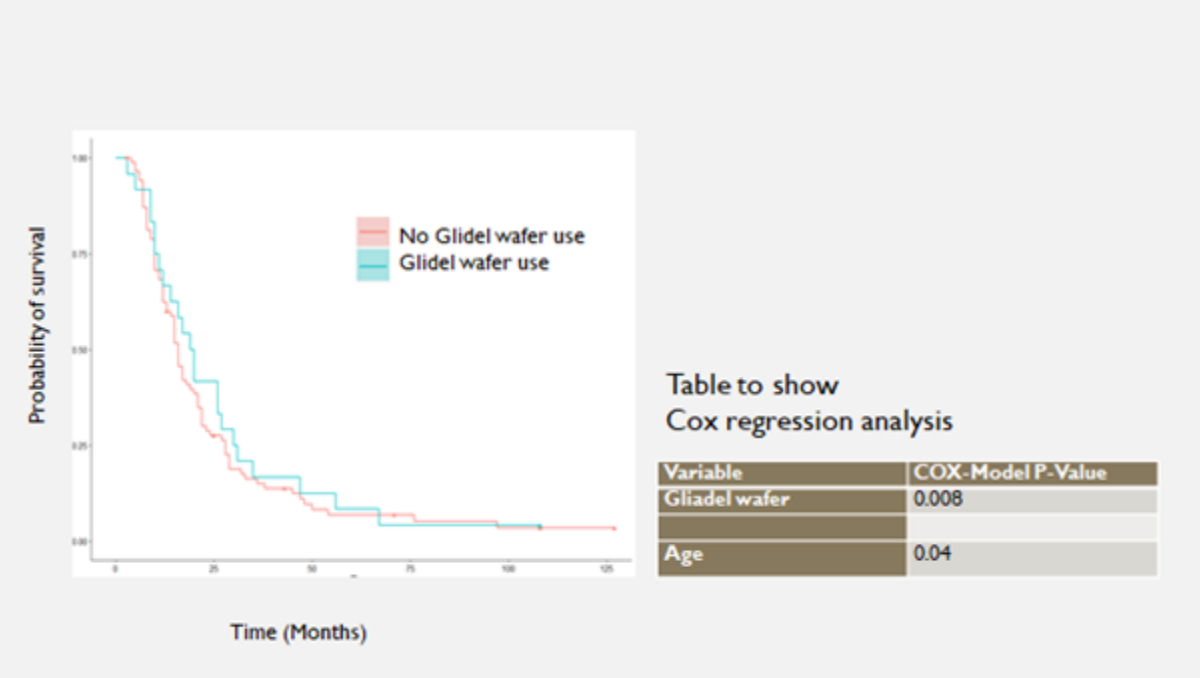

Figure 3: Kaplan–Meier plot to show OS for GBM with Maximal safe debulking with or without intra-operative Gliadel wafers.

Median PFS with the insertion of Gliadel wafers was 12.2 months (95% CI 10.43-19.7 months) and 11.8 months (95% CI 8.93-15 months) without. This was not statistically significant (Log Rank test P value 0.5). Of 110 patients 30% were Performance Status (PS) 0, 66% were PS 1 with only 3.6% being PS 2 (See Table 1 for raw data). 57% of patients completed adjuvant chemo-radiotherapy followed by 4-6 cycles of adjuvant TMZ and 43% received 3 or fewer cycles of TMZ. Of those that did not complete treatment the highest dropout rate was seen after the initial cycle of TMZ. Overall PFS was 12 months. Those that completed 4 or more cycles of adjuvant TMZ (n=64) had an improved PFS (Log-rank test P-value 0.001) versus those that completed 3 or fewer cycles (n=46) (See Figure 4). TMZ was discontinued due to clinical change, drop in performance status, deterioration in blood parameters on blood tests, and unacceptable toxicity.

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Median OS was 16 months for the whole group but improved to 20 months for those completing 4 or more cycles of adjuvant TMZ. Median OS decreased to 10 months for those unable to receive 4 cycles on TMZ. (See Figure 5) On Cox analysis, the number of adjuvant cycles of TMZ significantly affects OS, P-value 0.0003. Figure 5 demonstrates the lack of census points to allow 5-year OS to be reported for those receiving less than 5 cycles of TMZ (See Figure 5).

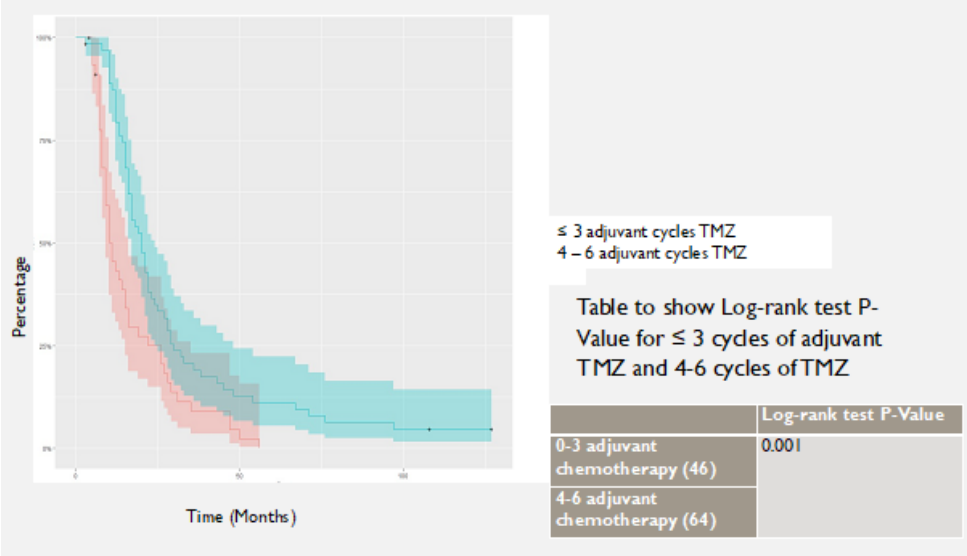

Figure 4: Kaplan–Meier plot to show PFS for GBM treated with ≤ 3 cycles of adjuvant TMZ and 4-6 cycles of TMZ at UHNM.

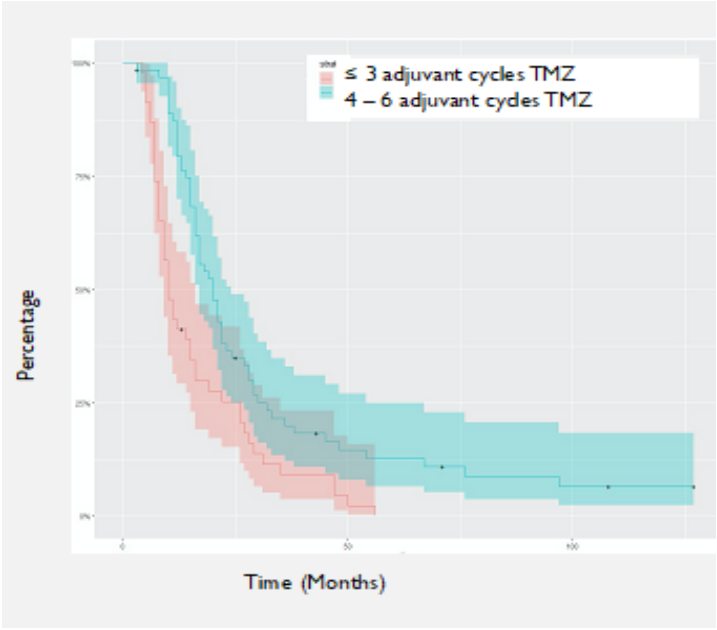

Figure 5: OS by Number of Adjuvant cycles received, Table to show log-rank test.

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Within the subset of 12 patients who had at least 4 cycles of adjuvant TMZ and Gliadel wafer insertion, the median OS was 18 months. An improvement of 2 months compared to those who received less than 4 cycles and did not have Gliadel wafers inserted. (OS 18 months vs 16 months, log-rank test P-value 0.4). Overall, 5-year survival rates are 5%. 95% relapsed within 5 years; at relapse, 20% underwent salvage surgery, and similar numbers 25%, received second-line chemotherapy.

Discussion

The data is presented from the long-term follow-up of 110 patients of the tertiary neuro-surgical center in the North Midlands, United Kingdom (UK).

The retrospective cohort includes those completing neurosurgery and chemoradiotherapy. Patients with surgical or radiotherapy complications from the cohort were excluded as this allowed the observation of the effects of completing adjuvant TMZ on survival outcomes.

The retrospective cohort from 2007-2016 yielded mature OS and PFS outcomes. However, the historical time frame led to heterogenous data due to the evolution of practice over time. So, firstly, patients who received reduced fractionation regimes were excluded. The cohort began before the publications by NCBTSG 2012 and Perry, et al trials [15-16] which have since led to more standardized hypofractionation radiotherapy practices for patients over 60 years and with performance status 2.

Secondly, MGMT, IDH, 19q16p codeletion and ATRIX biomarkers were not consistently carried out across this time period within the UK so data was not recorded. It is known those who are MGMT methylated have an improved prognosis and response to treatment [12] and so have been incorporated into the updated WHO classification in 2016 and 2021. The 2021 classification goes further to specify by IDH status, as IDH mutation incurs an improved survival outcome [17].

Overall, a median PFS of 11.9 months was demonstrated. PFS data has significant positive skewness statistically measured as 3.21, due to the statistical limitations of long-term retrospective cohorts. Therefore, the PFS is greater than the PFS of 6.9 months reported by the landmark Stupp trial. Stupp, et al., use intention-to-treat analysis, the retrospective cohort includes patients who have completed primary surgery and started chemoradiotherapy.

The median OS of 16 months was demonstrated. The median OS was 14.6 months within the Stupp trial once again, with analysis taken from the intention to treat the population [5]. A more recent retrospective cohort of GBM treated between 2007-2011 found a comparable median OS of 14.9 months in those receiving maximal treatment [1].

The age range within the cohort is 17-79 years, with a median age of 60 years. 4% of the cohort had a performance status of 2. This gives real-life data of GBM patients and makes direct comparisons to trial populations limited. Within the Stupp trial (those aged under 18-70 years and PS 2 or less) 85% completed planned chemoradiotherapy and adjuvant TMZ [5]. The real-world non-trial data demonstrated 57% of patients completed 6 cycles of TMZ following chemoradiotherapy. Patients did not complete 6 adjuvant cycles of TMZ for a variety of reasons, including infection, deterioration in performance status, toxicities, and progression. The reasons for

discontinuing adjuvant TMZ were not recorded within this study. This is a real-life clinical scenario; treatment is discontinued and here poorer outcomes in those patients were demonstrated.

For the first time patients receiving 4 or more cycles of adjuvant TMZ had an extra 10 months of median OS compared to those who received less than 4 cycles of adjuvant TMZ were demonstrated. This is a significant clinical and statistical difference. As clinically expected, if patients discontinued adjuvant TMZ it was most likely after the first cycle.

A second key finding was, in the center Gliadel wafer insertion improved OS by a median of 3.5 months, demonstrating those who do not have complications from Gliadel wafer insertion such as postoperative infection, incur a benefit.

Within the cohort, patients with Gliadel wafer insertion were observed and received 4 or more adjuvant cycles of TMZ to have improved OS. Therefore, the combination of both factors that would give maximal OS was hypothesized. Indeed, OS was improved by 2 months in this group. Statistical significance was not reached on the log-rank test (P-value 0.4) likely due to the small sample size of 12 patients.

95% of the cohort progressed despite primary standard treatment. At progression, 20% underwent re-do surgery and 25% had second-line chemotherapy with the majority opting for best supportive care (55%). This is comparable to the Stupp trial where 9.8%, survived 5 years and beyond, 23% underwent surgery, and 24% chemotherapy at relapse [5].

This review of data gives meaningful data to explain outcomes in the center and beyond.

Conclusions

- Overall, a median PFS of 11.9 months and a median OS of 16 months in the retrospective cohort of patients were demonstrated.
- Those receiving at least 4 cycles of adjuvant Temozolomide have improved overall survival by a margin of 10 months than those that discontinue Temozolomide due to unforeseen clinical circumstances.
- Gliadel wafer insertion, following at least 90% debulking at primary surgery, improves overall survival by a median of 3.5 months.
- The combination of both Gliadel wafer insertion and receiving at least 4 cycles of adjuvant Temozolomide improves overall survival on small subset analysis.

Data availability statement

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

The authors have no relevant financial or non-financial interests to disclose.

All data generated or analyzed during this study are included in this published article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. The datasets generated and analyzed during the current study are not publicly available due to confidential data being stored.

This is a retrospective observational study that used clinical records therefore ethical approval was sought. All authors were a part

of the clinical team and are bound by the General medical council.

Authors contributions statement

Dr. Ziff collected the data, Dr. Price wrote the main manuscript text, and Dr. Elmasry prepared the statistics. Dr. Giridharan oversaw the process and the cohort consisted of his patients. All authors reviewed the manuscript.

Accordance statement

Data were reviewed from surgical and oncology records. R-software V4.0.0 statistical package was used to carry out median, standard deviation, cox regression, or Log-rank analysis. All methods were performed in accordance with the relevant guidelines and regulations. All authors are bound by the principles of The General Medical Council UK. This retrospective cohort review has not been approved by a local ethics review committee, as data were retrospectively collected from existing clinical records by members of the clinical team. Stored on password-encrypted NHS devices. Data were not collected prospectively and therefore this retrospective review in no way affected decision-making and patient care.

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