Metastatic spine tumor epidemiology: comparison of trends in surgery across two decades and three continents.

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Abbreviations
EQ-5D Euroqol 5 Dimension 3 Level measure of health related quality of life
GSTSG Global Spine Tumour Study Group
Abstract

BACKGROUND

Indications for surgery for symptomatic spinal metastases have been better defined in recent years, and suitable outcome measures established, against a changing back-drop of patient characteristics, tumor behavior and oncological treatments. However variations still exist in the local management of patients with spinal metastases. The objective was to review global trends and habits in the surgical treatment of symptomatic spinal metastases, and how this has changed over the last 25 years.

METHODS

A cohort study of consecutive patients undergoing surgery for symptomatic spinal metastases. Data was collected using a secure internet database, in 22 centers across 3 continents. All patients were invited to take part in the study, unless unable or unwilling to give consent.

RESULTS

There was a higher incidence of colonic, liver, and lung carcinoma metastases in Asian countries, and more frequent presentation of breast, prostate, melanoma metastases in the West. Trends in surgical technique were broadly similar across the centers.

Overall survival rates after surgery were 53% (standard error 0.013) at 1 year, 31% (standard error 0.013) at 2 years, and 10% (standard error 0.013) at 5 years after surgery. Survival improved over successive time-periods, with longer survival in patients who received surgery in 2011-2016 compared to earlier time-periods.
CONCLUSION

Surgical habits have been fairly consistent between countries around the world, and over time. However, patient survival has improved in later years, which is perhaps due to medical advances in the treatment of cancer, improved patient selection, or operating earlier in the course of the disease.
Introduction

The contemporary spinal surgeon is becoming increasingly aware of spinal tumors: metastases are the most common neoplasm of the spine and will present in greater numbers as the global population ages.1 Due to differences in local management protocols, the decision to undergo surgery and choice of specific operations are likely to vary between geographic regions.

Published studies examining spinal metastases are largely limited to the experience of single centers utilizing a variety of tumor classification systems and outcomes measures, making it difficult to compare clinical practices.2-10 As a consequence, the differences in regional variations in the treatment of spinal metastases remain poorly documented.

The Global Spinal Tumour Study Group (GSTSG) maintains an international, prospectively collected dataset on the surgical treatment of spinal metastases employing a standardized classification system of surgical approaches and the EQ-5D health outcome measure to describe functional outcomes.2,11 Here, we describe the epidemiological characteristics, surgical management, and outcomes of spinal metastatic disease in ten countries throughout four different regions of the world to determine the variation in surgical trends over time and region.

Material and Methods

Inclusion/Exclusion Criteria

Patients diagnosed with spinal metastases between March 1991 and September 2016 at twenty-two referral centers in ten countries throughout Asia (China, Korea and Japan), mainland Europe (Belgium, Denmark, France, the Netherlands, Spain), the United Kingdom, and North America (Canada and the United States) were recruited for entry into the Global Spine Tumour Study
Group database. All patients underwent surgical intervention. Anonymized patient data was entered into the database directly by practitioners. Patients who were unable to provide consent for participation in research or had incomplete follow-up data (date of death or minimum two year follow-up) were excluded from the database. Ethical regulatory approval was obtained at each of the institutions contributing to the GSTSG database; all patients gave informed consent.

**Variables**

Clinical data collected included primary malignancy type, spinal levels involved, other sites of metastases (both visceral and extraspinal bone metastases), surgical approach, extent of resection performed, surgical details, quality of life at presentation as assessed by EQ-5D, Frankel score and survival. The extent of resection was stratified according to whether debulking, intrallesional corpectomy, or complete vertebrectomy was performed. The STROBE reporting guideline has been implemented in writing this manuscript.

**Statistical Analysis**

Descriptive statistical summary measures were used to assess relevant variables. Mean and standard deviation were calculated for continuous variables while binary and categorical variables were summarized by frequency and percentage. Kaplan-Meier survival estimators were fitted and curves were constructed. Values lower than P=.05 were considered significant. Data analysis was performed using Stata 13 software (StataCorp LLC, Texas USA).
Results

A total of 2148 patients with spinal metastases were admitted to participating referral centers between March 1991 and September 2016 (figure 1). Application of exclusion criteria yielded 2001 study participants (93.2%). The reasons for exclusion were incomplete follow-up in 5 patients (0.2%); insufficient patient details in one patient, and missing information on surgical approach in 141 patients (6.6%). The data was analyzed in four regions: the United Kingdom (UK), mainland Europe, North America, and Asia. The UK was considered in a separate category to mainland Europe due to anecdotal differences in surgical approach and management in comparison to other European centers.

Figure 1

Figure 2

There were substantial differences in the frequency of tumor types reported between Asia and other regions (figure 2). Asian centers diverged from prevailing trends with a higher frequency of colonic, liver, and lung carcinoma metastases, and a lower frequency of breast, prostate, melanoma metastases, and myeloma. Whereas regions outside of Asia reported liver carcinoma metastases in less than 5% of cases, these metastases were seen in Asian centers in 13% of patients. Similarly, lung carcinoma metastases were found in over a quarter (28%) of Asian referrals, despite rates ranging from 10 to 16% elsewhere. By contrast Asian centers had markedly lower rates of breast carcinoma metastases (6%) as compared with other regions, which reported 14-21% of referrals. This trend was also seen in myeloma where the rate in Asian centers (3%) was less than half that seen in mainland Europe and North America (Table 1).
Examining other regions polled revealed a lower incidence in presentation of metastatic prostate cancer in Asia and North America where rates of 5 and 7% (respectively) were substantially lower than those reported in Europe and the UK where it was found in 16-18% of cases. Sarcomas exhibited a unique trend with higher rates in UK and North America (3 and 5% respectively), than in Asia and Mainland Europe (2 and 1% respectively). Rates of lymphoma, renal, and other uncategorized metastases were similar across all regions.

Despite the differences in frequency of tumor types across regions, there was little variation in the male/female ratio with the percentage of male patients ranging from 55-60% globally (54.9% in the UK, 57.0% mainland Europe, 60.4% in Asia, 59.7% in North America). Similarly, the average age of patients at presentation ranged from 58-62 years across all regions (mean age 61.6 years in UK, 62.0 years Mainland Europe, 60.0 years Asia, 58.1 years in North America).

Table 1

Globally, the majority of surgery was performed via a posterior-only midline approach to the spine. Isolated posterior approaches were employed in 77% (in North America) to 94% of cases (in Asia). Combined anterior-posterior approaches to the spine, and anterior-only approaches, were the next most common, being employed less than 20% and 10% of the time respectively. Preoperative endovascular tumor embolization was employed in 10-22% of cases worldwide, and was performed in 9.6% of cases in the UK, 14.6% of cases in mainland Europe, 22.1% of cases in Asia, and 16.4% of cases in North America.
Trends in the extent of surgical resection differed between North American centers and other regions. In the UK, Europe, and Asia the majority of cases performed were piecemeal resections with the objective of palliative decompression (defined as <50% of tumor resected, as judged by the surgeon at the time of the operation, figure 3). In North America by contrast palliative decompressions were less frequently performed: the most commonly performed procedure in North American centers was piecemeal debulking of the metastatic lesion with greater than 50% of the lesion resected. For most regions, more palliative and debulking surgeries were performed, rather than complete corpectomies or en bloc resections. North American centers departed from this global trend in that a larger proportion of more aggressive resections were performed. In Asian centers piecemeal vertebrectomy was uncommon. As a result, resections in Asia can be largely dichotomized into piecemeal procedures or en bloc vertebrectomy, revealing a preference for en bloc resection when vertebrectomy was the objective.

The mean case duration differed little between regions, ranging from 3.3 to 3.8 hours globally. The distribution of case duration reveals that most cases were clustered around the overall mean of 3.5 hours in Mainland European (3.3 hours) and North American (3.6 hours) centers, but UK and Asian centers had a substantial proportion of cases that lasted longer than six hours in duration (mean duration 3.7 and 3.8 hours respectively).

Mean duration of stay on the spinal surgery ward varied between regions: In the UK, mean duration was 44 days (standard deviation SD 91 days); on Mainland Europe, mean 29 days.
(SD 213 days); in Asia, mean 28 days, (SD 31 days); and in North America, mean duration of
stay was 12 days (SD 28 days).

Pre-operative EQ-5D scores were similar between regions outside North America (UK
mean EQ-5D score of 0.39, mainland Europe mean 0.40, Asia mean 0.41). North American
patients reported significantly higher pre-operative EQ-5D scores with a mean value of 0.51.
Standard deviation was consistent for all regions, ranging from 0.28 in North America to 0.32 in
Asia.

Survival comparisons

Figure 4

Overall survival rates were 53% (standard error SE=0.013) at one year, 31% (SE=0.013) at two
years, and 10% (SE=0.013) at five years (figure 4).

An examination of two-year survival by region (figure 5) revealed that survival in the UK
and Mainland Europe differed from that in Asia and North America. (p<0.05). Two-year survival
in the UK was mean 26% (SE 3.0), mainland Europe was mean 28% (SE 2.0), Asia mean 52%
(SE 5.0) and North America mean 42% (SE 4.0).

Figure 5

Figure 6
Dividing study participants into four-year study periods based on year of surgery allowed an analysis of trends over time (figure 6). While one-year survival rates remained largely unchanged, survival rates beyond one year improved in patients diagnosed more recently. Compared to the baseline 1991-2000 group, there was a non-significant improvement in survival in the 2006-2010 group (P=.16), but significant improvements in the 2006-2010 (P=.02) and 2011-2016 groups (P<.01). This is particularly evident for the most recent group of patients recruited between 2011 and 2016 for which the Kaplan-Meier survival curve diverges from those of previous time periods.

The greatest difference in survival over the years was seen in the elderly population (71-80 years group) where there was better survival in elderly patients with metastatic disease in recent years (figure 7). Cox regression models of multiple variables revealed improved survival was related to the age at the time of surgery (P=.004) and the method of surgical tumor excision. Debulking and palliative surgeries were more frequently performed in recent years, and fewer en bloc excisional surgeries are now seen, as surgical philosophy has evolved from curative intent to improvement of quality of life (palliative surgery technique P<.01).

The neurological status at presentation as indicated by Frankel Grade improved over time, with a larger proportion of patients graded as Frankel E and a concomitant decrease in the proportion of Frankel grade C and D patients (table 2: In the 2011-16 group, 44.7% of patients presented with Frankel grade E, but only 25.6% of patients in the 1991-2001 group).
The mean age of patients at the time of diagnosis demonstrated little variation across time periods, averaging between 59.6 and 61.0 years of age. The extent of resection varied minimally over time with decompression or simple debulking representing the majority of cases (71.8-100%) and complete vertebrectomy being the objective in only a minority of cases (1.0-16%, table 3). Consistency was also observed in the relative proportions of primary tumor types over time: the three most common tumors reported across all time blocks were breast, renal, and lung carcinoma metastases, excluding cases in which there was no known histopathology (table 4).

Analyzing individual tumor types, there was a trend towards better survival in recent years for breast carcinoma metastases (figure 8, $P=.18$) and colorectal carcinoma metastases (figure 9, $P=.13$), but not statistically significant perhaps due to small sample size. However there was a significant improvement in survival after surgery for lung cancer (figure 10, $P=.04$). Other tumor types were not associated with improved survival in recent years.
Discussion

Regional differences in frequency of tumor types

In this study, the first global comparison of the surgical treatment of spinal metastases, we report wide variation in the frequency of metastatic tumor types between regions. The asymmetries observed in different parts of the world largely reflect those of primary cancer diagnoses in the respective regions. For example, the finding that Asian centers had higher numbers of GI, liver, and lung carcinoma metastases, reflects the high frequency of these primary cancers reported in Asia. Examining regional variations in the incidence of liver cancer in particular: of the over 750,000 new diagnoses of liver cancer made per year, China alone accounts for 50%. In comparison to other regions, the incidence of liver cancer in China is more than three times that in North America and ten times that in some European countries. The relatively small proportion of breast cancer metastases reported in Asian centers lends further support for this explanation, as epidemiological data reveals that the incidence of breast cancer in the United States is a multiple of that reported in most Asian countries.

This explanation however fails to account for certain regional variations seen in our study. Although Asian centers report the single largest proportion of spinal metastases in any region with lung cancer accounting for over a quarter of all spinal metastases, the incidence of primary lung cancer diagnoses is actually lower in China than it is in the United States. This unexpected finding may be in part due to early detection initiatives in the United States which call for regular radiographic screening of high risk patients, resulting in diagnosis of asymptomatic patients with isolated lung nodules before metastasis to distant sites can occur. It is also worth remembering that this study group represents only a subset of patients with spinal metastases in that it is limited to those who have undergone surgery for
treatment of their metastatic disease. Consequently, it may be the case that the advent and widespread availability of targeted therapies for lung cancer in the United States is resulting in better medical control and fewer surgical referrals.\textsuperscript{18} Taken together, these considerations illustrate that there is no simple or straightforward explanation for the different rates of primary tumors metastasizing to the spine. Rather the interplay between regional primary cancer rates, cancer screening protocols enabling early detection prior to distant spread, and access to advanced oncological therapies, probably contribute to produce the regional variations we report here.

**Survival analysis**

Examining the results of our survival analysis with respect to the year of diagnosis reveals that long-term survival improved over the time course of this study. Despite the fact that one year survival remained largely unchanged from 1991 to 2016, the Kaplan-Meier survival curve for the most recent quartile (2011-2016) diverged significantly from those representing earlier time periods. The reasons behind this improvement in long-term survival are difficult to determine with certainty, but the fact that the surgical approaches employed and the extent of resection achieved throughout the time periods analyzed remained the same suggests that the improvements demonstrated here are not attributable to differences in surgical treatment. Rather, it is more likely that the gains achieved in long-term survival reflect a combination of earlier detection,\textsuperscript{15,16} more efficacious adjuvant medical therapies,\textsuperscript{19,20,21,22} and a better understanding of spinal metastatic disease leading to selection of patients better suited for surgery with a greater potential for long term survival.\textsuperscript{10} Changes in the medical management of lung cancer are likely to be responsible for better survival in recent years (figure 10), and similar trends were seen in
patients with spinal metastases due to breast or colorectal carcinomas (figures 8,9). The improvement in survival in more elderly groups may be due to a combination of better medical treatments and more palliative, less extensive (and therefore complicated) surgeries which have been performed in recent years.

**EQ-5D**

North American centers reported significantly higher pre-operative EQ-5D scores than in other parts of the world. This finding could be interpreted as evidence of earlier detection, more timely referrals, or a preference for surgical treatment. Alternatively, this may not reflect a genuine functional difference but instead could be attributed to recognized differences in how patients from different regions self-assess well-being. The purpose of country-specific preference weights as applied to the EQ-5D scoring system is to account for known differences in self-assessment and to normalize them to facilitate accurate cross-cultural comparisons. In an examination of US, UK, and Japanese EQ-5D country-specific preference weights as applied to a Thai population of type 2 diabetic patients, Sakthong et al found that application of US preference weights yielded higher scores than the UK or Japanese preference weights.\(^{23}\) Whether the higher preoperative EQ-5D scores in US patients reported here is artefactual or attributable to genuine differences in practice is difficult to say.

**Limitations**

Our database is subject to inherent limitations which may impact the generalizability of our conclusions. Given that our dataset is composed exclusively of surgical patients, all non-surgically treated patients were excluded from our analyses. Patients with poor prognoses are
typically not considered candidates for surgery, so a focused analysis of surgically treated patients may introduce a selection bias whereby study participants represent a subset of patients with better prognosis than the population of patients with spinal metastases at large. The data in this study was entirely self-reported, and as such is susceptible to reporting bias. This is particularly true for the extent of resection, which was based on each individual surgeon’s estimation of the overall percentage of the lesion resected rather than objective radiological criteria. The surgical practice of individual centers may vary, and inclusion of data from units with a preference for more complete or aggressive surgery may bias the results. Lastly, the prospective collection of data over the span of more than a decade means that data was collected at different points in time.

Conclusions

In this first global comparison of the epidemiology, surgical approaches, and long-term survival in patients undergoing surgery for treatment of spinal metastases we find substantial regional variation in the composition of primary tumor types leading to spinal metastatic disease despite uniformity in the preferred surgical approach, surgical objectives, and long-term survival. The regional variation reported here should lend further support for global collaboration, as what is considered a rare metastasis for some may be commonplace for others. On a local scale, this data should prompt surgeons to seek out oncologists with particular expertise in managing the metastases that present most frequently in their region.

The long-term survival data reported here reveals that patients with spinal metastases are living longer. This improvement in long-term survival should prompt reconsideration of our surgical decision-making processes. Many of the prognostic scoring algorithms that we employ
in patient selection for surgery were constructed on data gathered more than a decade prior. Given the improved long-term survival we report from 2011-2015, surgeons should be wary of using these prognostic scoring systems, which might exclude patients from surgery on the basis of predictions calculated using old data.

Surgery for spinal metastases can improve pain, deformity, and neurological function.24 It is well recognized that multidisciplinary team discussion is paramount in formulating treatment strategies that yield the best outcomes for patients. Patients with spinal metastases are now living longer without any change in surgical management, suggesting that this enhanced survival is largely due to advances in medical therapy and radiation techniques. Consequently, the survival benefit reported here should be interpreted as further support for a collaborative approach towards the management of spinal metastases relying on expertise in oncology, surgery, and radiotherapy, to offer an integrated and personalized treatment for patients.

Figure Captions

Figure 1: Consort flow diagram for patient recruitment and exclusion.
Figure 2: Tumor types in different regions.
Figure 3: Type of surgery performed in different regions.
Figure 4: Overall survival after surgery.

Figure 5: Survival after surgery in different geographical regions.
Figure 6: Survival after surgery for successive 5 year recruitment periods, demonstrating improving outcomes.

Figure 7: Survival over successive 5 year periods in patients who are aged between 71 and 80 years.
Figure 8: Survival over time, for breast carcinoma metastases to the spine.

Figure 9: Survival over time, for colorectal carcinoma metastases to the spine.
Figure 10: Improved survival over time, for lung cancer metastases to the spine.

Table Captions

Table 1: Tumor type by global area (numbers and percentages). Missing n=63 (3.2%)

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>UK</th>
<th>Mainland</th>
<th>Asia</th>
<th>North America</th>
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<td></td>
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<td>7</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>16</td>
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<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>Bladder</td>
<td>4 (0.8)</td>
<td>15 (1.5)</td>
<td>2 (0.9)</td>
<td>8 (3.6)</td>
<td>29 (1.5)</td>
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<td>Breast</td>
<td>97 (20.0)</td>
<td>217 (21.5)</td>
<td>13 (5.9)</td>
<td>31 (14.0)</td>
<td>358 (18.5)</td>
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<td>Cervical</td>
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<td>12 (1.2)</td>
<td>0 (0)</td>
<td>3 (1.4)</td>
<td>18 (0.9)</td>
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<tr>
<td>Colon</td>
<td>20 (4.1)</td>
<td>49 (4.9)</td>
<td>14 (6.4)</td>
<td>7 (3.2)</td>
<td>90 (4.6)</td>
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<tr>
<td>Gastric</td>
<td>9 (1.9)</td>
<td>16 (1.6)</td>
<td>5 (2.3)</td>
<td>3 (1.4)</td>
<td>33 (1.7)</td>
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<tr>
<td>Liver</td>
<td>5 (1.0)</td>
<td>7 (0.7)</td>
<td>29 (13.2)</td>
<td>12 (5.4)</td>
<td>53 (2.7)</td>
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<td>Lung</td>
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<td>121 (12.0)</td>
<td>62 (28.1)</td>
<td>36 (16.3)</td>
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<td>13 (1.3)</td>
<td>7 (3.2)</td>
<td>7 (3.2)</td>
<td>33 (1.7)</td>
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<td>Melanoma</td>
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<td>35 (1.8)</td>
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<td>Myeloma</td>
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<td>69 (6.8)</td>
<td>7 (3.2)</td>
<td>15 (6.8)</td>
<td>115 (5.9)</td>
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<td>Other</td>
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<td>57 (5.6)</td>
<td>18 (8.2)</td>
<td>25 (11.3)</td>
<td>129 (6.7)</td>
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<td>Prostate</td>
<td>77 (15.8)</td>
<td>184 (18.2)</td>
<td>10 (4.6)</td>
<td>15 (6.8)</td>
<td>286 (14.8)</td>
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<td>Renal</td>
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<td>113 (11.2)</td>
<td>24 (10.9)</td>
<td>29 (13.1)</td>
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<td>Sarcoma</td>
<td>13 (2.7)</td>
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<td>4 (1.8)</td>
<td>5 (2.3)</td>
<td>156 (8.1)</td>
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<td>Total</td>
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<td>1011 (100.0)</td>
<td>220 (100.0)</td>
<td>221 (100.0)</td>
<td>1938 (100.0)</td>
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Table 2: Frankel grade by year (numbers and percentages). Missing n=14 (0.7%)

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<td>8 (2.0)</td>
<td>18 (1.6)</td>
<td>30 (1.5)</td>
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<tr>
<td>B</td>
<td>2 (4.7)</td>
<td>9 (2.3)</td>
<td>18 (4.4)</td>
<td>45 (4.0)</td>
<td>74 (3.7)</td>
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<tr>
<td>C</td>
<td>14 (32.6)</td>
<td>102 (25.6)</td>
<td>81 (20.0)</td>
<td>220 (19.3)</td>
<td>417 (21.0)</td>
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<tr>
<td>D</td>
<td>16 (37.2)</td>
<td>150 (37.7)</td>
<td>144 (35.5)</td>
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<td>133 (33.4)</td>
<td>155 (38.2)</td>
<td>509 (44.7)</td>
<td>808 (40.7)</td>
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<td>406 (100.0)</td>
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Table 3: Extent of excision by year (numbers and percentages). Missing n=189 (9.5%)
Table 4: Comparison of the presenting tumour types in different time periods (numbers and percentages). Missing n=63 (3.2%)

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