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Long-term outcomes of pulmonary metastasectomy:

A multi-centre analysis

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Abstract

Introduction

Many extra-pulmonary neoplasms metastasise to the lungs. We conducted a retrospective review of all patients who underwent pulmonary metastasectomy for oligometastatic disease at two centres in order to determine long-term outcomes.

Methods

The study institutions' thoracic surgery databases were searched for all patients who underwent pulmonary metastasectomy from 2000 - 2017.

Results

There were a total of 476 patients who underwent pulmonary metastasectomy. Mean age at time of surgery was 57.2 ± 15.9 years. Mean number of pulmonary lesions was 1.9 ± 1.6. Mean disease free interval (DFI) was 3.6 ± 4.3 years. The most common primary neoplasms were colorectal cancer (CRC) in 35.1% (167/476), sarcoma in 23.9% (114/476), melanoma in 16.2% (77/478), renal cell carcinoma (RCC) in 7.3% (35/476) and germ cell tumour (GCT) in 4.4% (21/476).

Hospital mortality was 0.4% (2/476). Mean follow-up time was 3.8 ± 2.9 years. Survival was 88.9% (95%CI: 85.77 – 91.5%) at 1-year and 49.6% (95%CI: 44.4 – 54.6%) at 5-years. On multivariate Cox-regression analysis GCT (P = 0.004), CRC (P = 0.03), DFI of 36+ months (P = 0.007), R0 resection (P = 0.002) and non-anatomical, sub-lobar (wedge) resection (P = 0.002) were protective against mortality.

Conclusion

Pulmonary metastasectomy is associated with survival of 50% at 5-years follow-up. DFI of over 36 months, R0 resections, lesions resectable by wedge resection rather than anatomic resection and GCT and CRC primary cancers were associated with improved survival.

Key words: Metastasectomy, Video Assisted Thoracoscopic Surgery, Metastasis

Introduction

Many extra-pulmonary neoplasms metastasise to lungs (1). Surgical resection of pulmonary metastases has been widely practiced for many years (2). The prognosis of patients with pulmonary metastases remains poor with reported 10-year survival of 26-27% (2, 3). Pulmonary metastasectomy has been shown to be beneficial in select groups of patients (4, 5). However, attempts to perform prospective, randomized control trials to assess the efficacy of pulmonary metastasectomy have so far proven unsuccessful (6). Changing trends in oncological treatments have and will continue to alter pre-existing surgical interventions for pulmonary metastases (7). We conducted a retrospective review of all patients who underwent pulmonary metastasectomy for oligometastatic disease at two centres in order to determine long-term outcomes.

Methods

Ethics

Research ethics was attained via study institutions' Research Governance Unit (QA 2018144 and LRR 138/15)

Patients

Our 2 institutional thoracic surgical databases were retrospectively analysed and all cases with pulmonary metastasectomy for oligometastatic disease from 2000 – 2017 were included. The patients and public were not involved in the design, conduct and reporting of the research.

Definitions

Oligometastatic was defined as metastasis to a single organ system. Hospital mortality was defined as mortality occurring during the admission for surgical

metastasectomy or within 30 days of surgery. Late mortality was defined as mortality occurring greater than 30 days after discharge from hospital. Late re-operation was defined as repeat pulmonary resection occurring greater than 90 days after initial pulmonary metastasectomy. Disease free interval (DFI) was defined as the period between first cancer diagnosis and first pulmonary metastasectomy. Thoracotomy was defined as any surgical access requiring rib spreading. Wedge resection was defined as a non-anatomical, sub-lobar lung resection. Segmentectomy was defined as an anatomical sub-lobar resection. Treatment of melanoma was divided into two eras – the first predating the introduction of targeted therapies for melanoma and the second following the Pharmaceutical Benefit Scheme (PBS) listing of these targeted therapies in August 2013 (8). These were analysed separately as the advances in systemic therapy in this time have transformed outcomes in advanced malignant melanoma. Complete (R0) resection was defined as a surgical specimen that was clear of microscopic margins.

Statistical analysis

Data was sourced from hospital medical records and lung cancer databases. Statistical analysis was performed with STATA version 15 (Stata Corp, College Station, TX, USA). Unless otherwise stated, continuous data were summarised as mean ± standard deviation. The time dependant end points were all-cause mortality and late re-operation. Cox proportional hazards analysis was used to examine risk factors for mortality. Univariate analysis was performed and variables with moderate evidence against the null hypothesis ($P < 0.1$) were included in the multivariate model.

Results

A total of 476 patients underwent pulmonary metastasectomy for oligometastatic disease between 2000 and 2017. Mean patient age at the time of first lung resection was 57.25 ± 15.92 years. Mean disease free interval was 3.58 ± 4.30 years. Mean number of lesions at time of first pulmonary metastasis was 1.86 ± 1.62. Multiple pulmonary nodules at the time of first pulmonary metastasis were present in 41.6% (198/476) of patients. Bilateral pulmonary lesions were present in 14.08% (67/476) of patients at the time of first lung resection. A full list of demographics can be found in **table 1**.

Surgery

There were a total of 827 pulmonary metastasectomies performed on 476 patients. Minimally invasive access via video assisted thoracoscopic surgery (VATS) was used in 84.66% (403/476) of patients. Thoracotomy was used in 15.34% (73/476) of patients. The types of resection performed were wedge resection in 72.90% (347/476), segmentectomy in 7.56% (36/476), lobectomy in 21.01% (100/476) and pneumonectomy in 1.05% (5/476) of patients. An R0 resection was achieved in 97.69% of patients (465/476).

Primary neoplasms

The primary neoplasms were colorectal cancer (CRC) in 35.08% (167/476), sarcoma in 23.95% (114/476), melanoma in 16.18% (77/476), renal cell carcinoma (RCC) in 7.35% (35/476), germ cell tumour (GCT) in 4.41% (21/476), breast in 2.52% (12/476), head and neck in 2.52% (12/476) and other uncommon neoplasms in 7.98% (38/476). Of the 77 melanoma patients, 72.73% (56/77) underwent metastasectomy in era 1 prior to the introduction of immune checkpoint inhibitors and BRAF inhibitors. The remaining 21 (27.27%, 21/77) underwent metastasectomy in era 2 following the introduction of immune checkpoint inhibitors and BRAF inhibitors. Of the GCT patients the final histopathology showed mature teratoma in 57.14 %

(12/21), yolk sac or mixed in 38.09% (8/12) and necrotic debris in 4.76% (1/21). A full list of primary neoplasms can be found in **table 2**.

Mortality and follow-up

Hospital mortality was 0.43% (2/476). Follow-up was 98.74% complete (470/476). Median follow-up time was 5.90 years (IQR 3.24 – 8.38 years). Late mortality occurred in 49.14% (230/468) of patients. Survival estimates were 88.99% (95%CI: 85.77 – 91.52%) at 1-year, 49.60% (95%CI: 44.37 – 54.60%) at 5-years and 32.28% (95%CI: 25.71 – 39.02%) at 10-years (**figure 1**). Survival estimates by primary neoplasm were – CRC: 95.69% (95%CI: 91.97-97.92%) at 1-year, 56.58% (95%CI: 47.36-64.98%) at 5-years and 39.28% (95%CI: 27.43-50.91%) at 10-years; Sarcoma: 83.30% (95%CI: 75.07-89.00%) at 1-year, 42.51% (95%CI: 32.72-51.94%) at 5-years and 26.40% (95%CI: 16.06-37.91%) at 10-years; Melanoma era 1: 80.36% (95%CI: 67.34-88.61%) at 1-year, 34.96% (95%CI: 22.64-47.53%) at 5-years and 21.51% (95%CI: 8.41-38.52%) at 10-years; Melanoma era 2: 89.95 (95%CI: 65.34-97.40%); Others: 89.20% (95%CI: 81.76-93.72%) at 1-year, 55.20% (95%CI: 43.90-65.13%) at 5-years and 35.88% (95%CI: 22.81-49.12%) at 10-years (**figure 2**).

Risk factors for mortality

On univariate analysis CRC (P = 0.002, HR 0.64), GCT (P = 0.007, HR 0.21), R0 resection (P = 0.001, HR 0.33) and wedge resection (P = 0.017, HR 0.71) were associated with prolonged survival. Melanoma era 1 (P = 0.005, HR 1.63) and sarcoma (P = 0.025, HR = 1.38) were risk factors for mortality. DFI of 36+ months (P = 0.08, HR 0.79) had a direction of effect associated with prolonged survival and multiple lesions at the time of first resection (P = 0.053, HR 1.29) demonstrated a direction of effect associated with earlier mortality with neither being statistically

significant. They were included in the multivariate analysis. Other factors that were not statistically significant on univariate analysis have been outlined in **table 3**.

On multivariate analysis GCT (P = 0.004, HR 0.18), CRC (P = 0.034, HR 0.67), DFI of 36+ months (P = 0.006, HR 0.68), R0 resection (P = 0.002, HR 0.33) and wedge resection (P = 0.019, HR 0.72) were associated with prolonged survival (**table 3**).

Re-operation

Repeat pulmonary metastasectomy occurred in 21.87% (103/471) of patients. Late re-operation occurred in 20.43% (96/470). Freedom from late re-operation estimates were 90.12% (95%CI 86.90 – 92.58%) at 1-year, 72.27% (95%CI 66.64 – 77.11%) at 5-years and 68.14% (60.56 – 74.57%) at 10-years (**figure 3**). The statistical analysis for risk of late re-operation has been outlined in **table 4**. Cox proportional hazards analysis revealed no factors predictive of late re-operation.

Discussion

Traditionally, the long-term prognosis of any metastatic cancer was considered poor. However, there have been a number of studies that have suggested that aggressively treating pulmonary metastases with surgical resection may provide a benefit in select patients (2-5, 9). However, oncological interventions are continually evolving and the literature must be updated to reflect changing trends in management of pulmonary metastases..

While pulmonary metastasectomy is a safe procedure that may benefit a large population of patients there is still a lack of evidence from randomised control trials. Treasure and colleagues (6) attempted to address this issue with a randomised

control study comparing pulmonary metastasectomy with active monitoring to active monitoring alone in patients with metastatic CRC. They reported 5-year survival estimates of 38% in patients undergoing metastasectomy and 29% in patients undergoing active monitoring alone. However, this study was unable to recruit adequately and was stopped early. Although the 9% difference in survival was not statistically significant it may simply be due to inadequate power due to the low recruitment. While there is a lack of good quality, randomised control data regarding pulmonary metastasectomy, the experience of Treasure and colleagues (6) demonstrates the difficulty in performing a study that randomises a group of patients to no intervention when that intervention can be performed safely and has some evidence suggesting benefit, albeit from low-quality, retrospective cohort analyses (2, 3, 5, 9). This lack of randomised data, as well as the lack of up-to-date data regarding the benefit of surgery versus newer targeted therapies such as tyrosine kinase inhibitors and immunotherapy is the greatest challenge faced by surgeons when making decisions in caring for these patients.

Our data has the same inherent flaws and limitations that are widespread in the literature on pulmonary metastasectomy and we hope to have more mature data on the use of systemic therapies in addition to metastasectomy in future publications. However, in the absence of randomised data, while waiting for high-quality prospective registry data to be collected, we present our retrospective experience and attempt to shed further light on this topic.

Throughout the published literature there are many prognostic factors that influence survival following pulmonary metastasectomy (2, 3, 9, 12). Among our cohort on multivariate analysis, DFI of 36+ months, R0 resection, wedge resection, GCT and CRC were found to be protective against mortality. Across multiple published series DFI of 36+ months has consistently been shown to be protective against mortality

(12). This may reflect a more indolent tumour biology and the associated improved outcomes. Obtaining an R0 resection remains a critical component of surgery for pulmonary metastatic disease. This is in line with findings from numerous publications that have found incomplete resection is a significant risk factor for mortality (2, 3, 9). Lesions that were able to be resected by wedge resection rather than those requiring anatomic resection were more likely to have better long-term survival. We infer from this that the poorer outcomes associated with segmentectomy, lobectomy and pneumonectomy was due to their more central location, larger size or more invasive nature.

Although, among our GCT group there was only one patient with necrotic debris on histopathology there was also a high proportion of mature teratoma in resected specimens (57%). This could explain the improved survival in this group. CRC was the most common primary cancer in our cohort and is one of the most common primary cancers that metastasize to lung as reported by the literature (12). Younes and colleagues (9) reported better survival rates among the patients with CRC, however it was not statistically significant on multivariate analysis. Other large series have not shown a survival advantage from CRC when compared to other primary cancers (2, 3). This may represent advances in systemic therapy for CRC over sarcoma and highlight the importance of multidisciplinary approach to these patients.

Conclusions

Our series updates the international literature and confirms the feasibility of performing safe, minimally invasive pulmonary metastasectomy with very high rates of R0 resection. The factors associated with better long term oncological outcomes were unsurprisingly, factors that aligned with less aggressive tumour biology – those with a DFI of 36 months or more, those resectable with clear margins, and those

resectable by wedge resection rather than anatomic resection (by which we infer as smaller, more peripheral tumours). Patients with GCT and CRC had better survival than those with sarcoma, melanoma or other tumour types.

As such, we advocate for the ongoing role of pulmonary metastasectomy in the treatment of carefully selected patients with oligometastatic disease. The failure to recruit for randomised trials in this space suggests that the next step should be carefully maintained prospective registries of patients undergoing pulmonary metastasectomy, complete with molecular analysis of resected specimens, of patients undergoing pulmonary metastasectomy so we can continue to advance the care of this challenging group of patients.

Funding statements

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Conflicts of interest

None declared.

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Figures

Figure 1: Kaplan-Meier survival estimates

Figure 2: Kaplan-Meier survival estimate by neoplasm

Figure 3: Kaplan-Meier freedom from late re-operation estimates

Tables

Table 1. Patient characteristics

Variable	Number of patients (%)
Total	476
Total number of operations	827
Male/Female	270 (56.72)/ 206 (43.28)
Age at first pulmonary metastasectomy	57.25 ± 15.92 years
DFI 0-11 months	102 (21.43)
DFI 12-23 months	111 (23.32)
DFI 24-35 months	78 (16.39)
DFI 36+ months	185 (38.87)
Right lung lesion	283 (59.45)
Left lung lesion	260 (54.62)
Bilateral lesions	67 (14.08)
Multiple pulmonary nodules	198 (41.6)
VATS	403 (84.66)
Thoracotomy	73 (15.34)
Wedge resection	347 (72.90)
Segmentectomy	36 (7.56)
Lobectomy	100 (21.01)
Pneumonectomy	5 (1.05)
R0 resection	465 (97.69)
Complete follow up	470 (98.74)
Follow-up time	3.77 ± 2.89 years
Hospital mortality	2 (0.43)
Late mortality	230 (49.14)
Late re-operation	96 (20.43)

DFI: disease free interval; VATS: video assisted thoracoscopic surgery

Table 2. Primary neoplasms

Primary cancer	**Number of patients (%)**
Colorectal	167 (35.08)
Sarcoma	114 (23.95)
Melanoma	77 (16.18)
Renal Cell Carcinoma	35 (7.35)
Germ Cell Tumour	21 (4.41)
Breast	12 (2.52)
Head and Neck	12 (2.52)
Uncommon	
Anal	1 (0.21)
Cholangeocarcinoma	1 (.021)
Bladder	3 (0.63)
Abdominal carcinoid	2 (0.42)
Cervical	5 (1.05)
Endometrial	3 (0.63)
Oesophageal	5 (1.05)
Pancreatic	3 (0.63)
Pecoma	1 (0.21)
Penile	1 (0.21)
Prostate	5 (1.05)
Pseudomyxoma peritonei	1 (0.21)
Skin	4 (0.84)
Testicular	1 (0.21)
Thymoma	2 (0.42)

Table 3. Cox-Hazards analysis for mortality

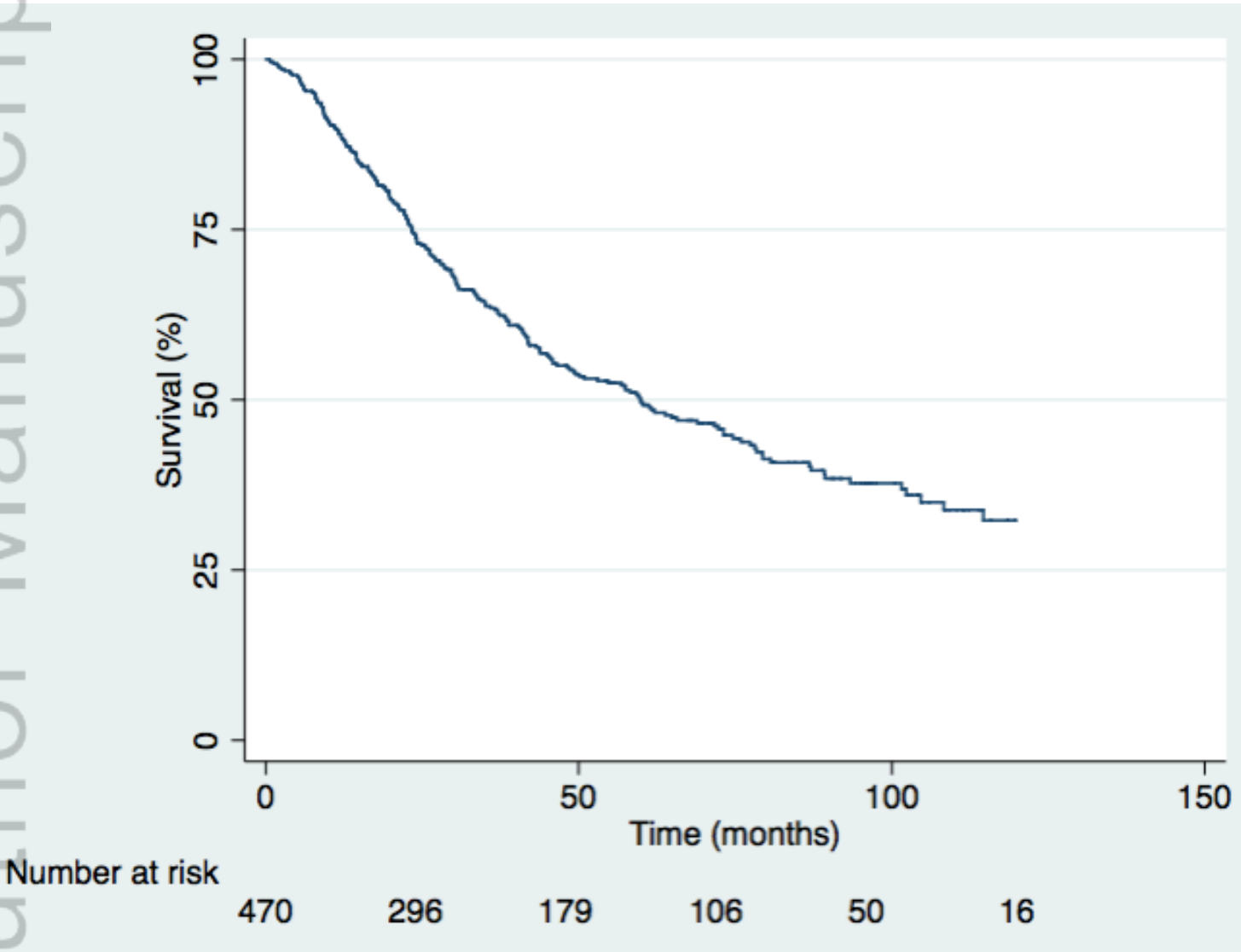
Variable	Univariate analysis	Multivariate analysis		
	P value	P value	Hazards ratio	95% CI
Increasing age	0.315			
DFI 0-11 months	0.210			
DFI 12-23 months	0.510			
DFI 24-35 months	0.825			
DFI 36+ months	0.082	0.007	0.68	0.52 – 0.90
CRC	0.002	0.034	0.67	0.46 – 0.97
Melanoma Era 1	0.005	0.127	1.39	0.91 – 2.11
Melanoma Era 2	0.596			
Sarcoma	0.025	0.754	1.06	0.73 – 1.54
RCC	0.696			
Breast	0.683			
GCT	0.007	0.004	0.17	0.05 – 0.56
Head and Neck	0.704			
Uncommon	0.528			
Multiple lesions	0.053	0.071	1.29	0.98 – 1.69
Bilateral lesions	0.923			
VATS	0.111			
Thoracotomy	0.111			
Wedge resection	0.017	0.022	0.72	0.55 – 0.95
Segmentectomy	0.387			
Lobectomy	0.211			
Pneumonectomy	0.628			
R0 resection	0.001	0.002	0.33	0.17 – 0.67
Repeat metastasectomy	0.402			

CRC = colorectal cancer; DFI: disease free interval; GCT: germ cell tumour; RCC: renal cell carcinoma; VATS: video assisted thoracoscopic surgery

Table 4. Cox-Hazards analysis for late re-operation

Variable	Univariate analysis	Multivariate analysis		
	P value	**P value**	**Hazards ratio**	**95% CI**
Increasing age	0.037	0.654	1.00	0.98 – 1.01
DFI 0-11 months	0.340			
DFI 12-23 months	0.409			
DFI 24-35 months	0.081	0.095	1.52	0.93 – 2.50
DFI 36+ months	0.243			
CRC	0.544			
Melanoma era 1	0.068	0.680	1.56	0.19 – 13.07
Melanoma era 2	0.209			
Sarcoma	0.001	0.131	1.42	0.90 – 2.24
RCC	0.345			
Breast	None observed			
GCT	0.188			
Head and Neck	0.788			
Uncommon	0.073	0.156	0.43	0.13 – 1.38
Multiple lesions	0.0001	0.108	1.50	0.92 – 2.46
Bilateral lesions	0.0001	0.055	1.68	0.99 – 2.87
VATS	0.721			
Thoracotomy	0.721			
Wedge resection	0.276			
Segmentectomy	0.775			
Lobectomy	0.368			
Pneumonectomy	0.109			
R0 resection	0.767			

CRC = colorectal cancer; DFI: disease free interval; GCT: germ cell tumour; RCC: renal cell carcinoma; VATS: video assisted thoracoscopic surgery



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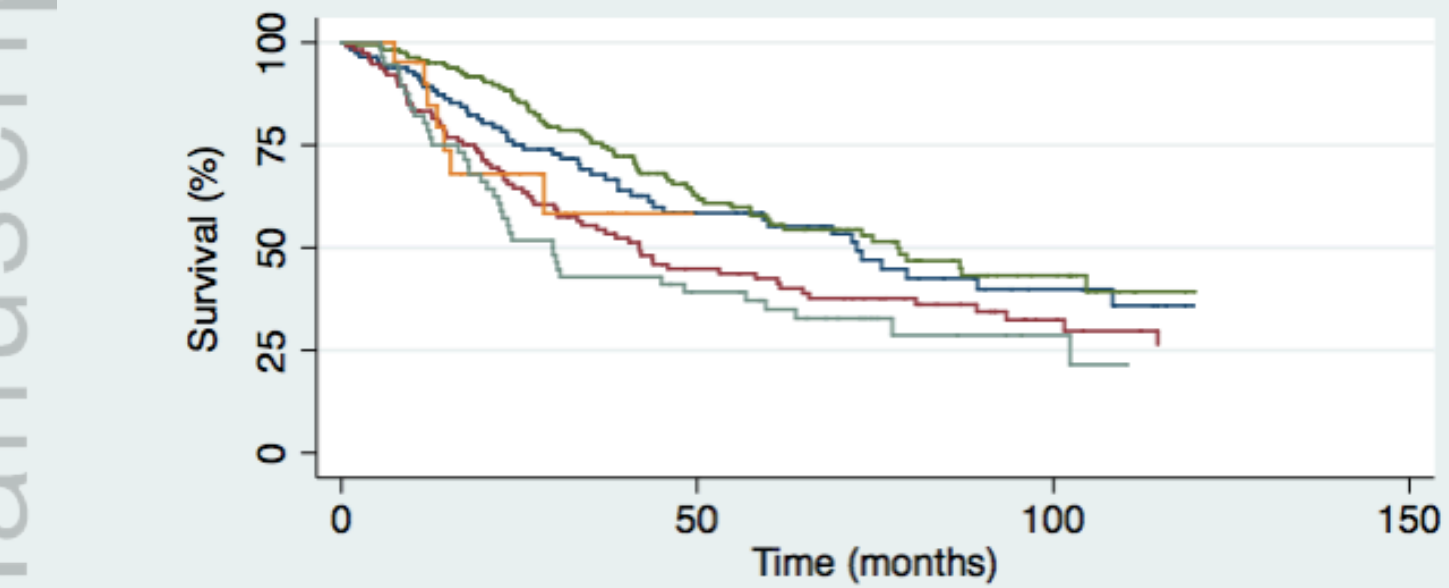

Number at risk

Other	114	72	41	26	13	3
Sarcoma	114	66	41	29	15	8
Colorectal	165	120	74	39	18	3
Melanoma Era 2	21	9	1	0	0	0
Melanoma Era 1	56	29	22	12	4	2

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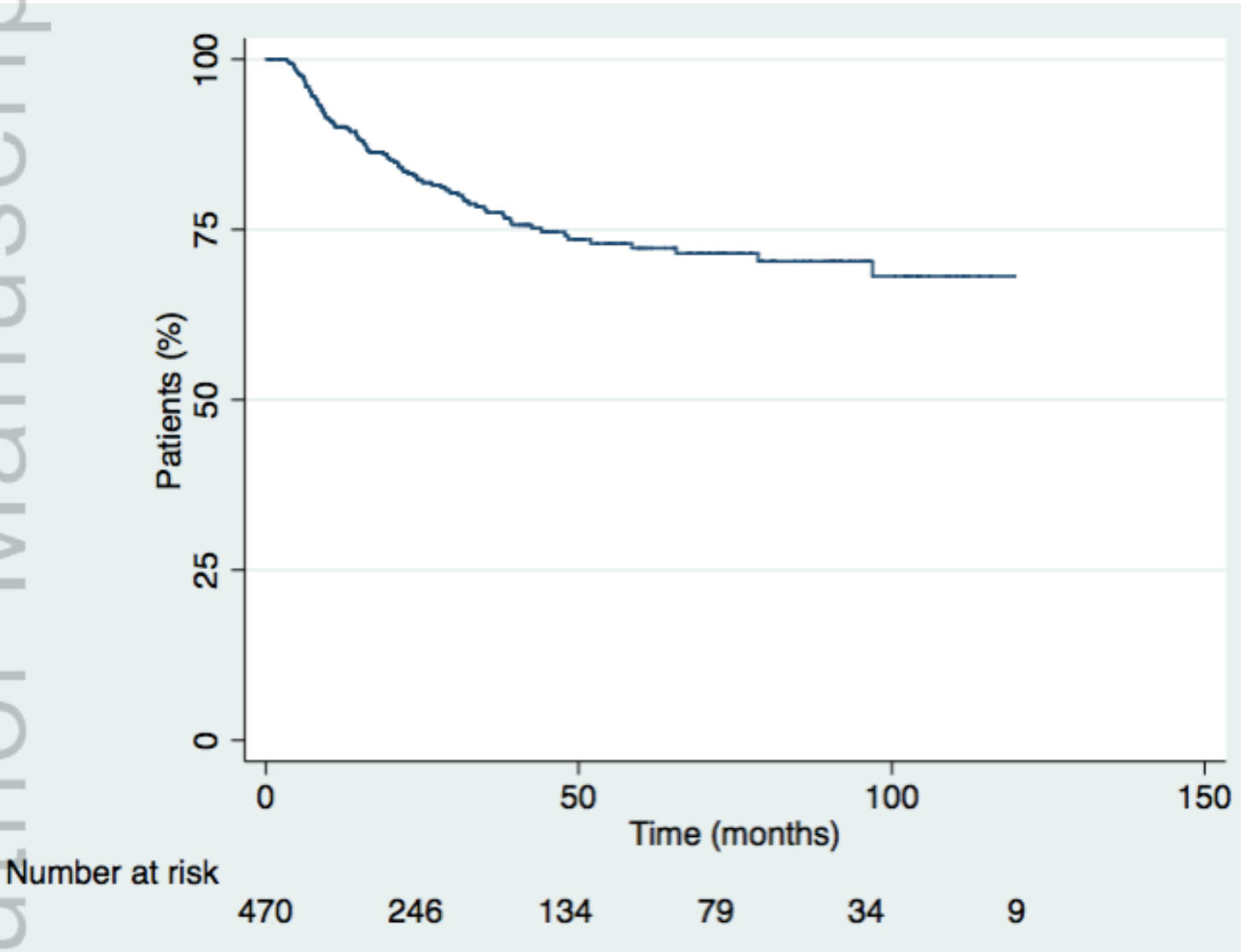

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