



Orbital exenteration: tumour diversity and survival in a tertiary referral centre

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Background: Orbital exenteration (OE) is performed in the context of peri-orbital or orbital malignancy, or life-threatening orbit-involving infections. The survival of patients undergoing OE for malignancy is varied in the literature. Histopathological heterogeneity has been described highlighting the complexity of orbital involving tumours. We describe our experience with OE in a metropolitan tertiary referral centre.

Methods: A retrospective chart review of medical records, imaging, pathology and existing databases was performed of patients who underwent OE between January 2005 and December 2015. Disease free survival (DFS) and overall survival (OS) were calculated and Kaplan Meier survival curves generated. Subgroup analysis was performed of tumour subgroups for squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and other tumour types.

Results: Thirty-five orbits of 35 patients were included. Median age at OE was 69.4 years. 10 tumour types were identified. Fifteen patients underwent OE for SCC, 6 for BCC and 14 for other tumour types. Mean DFS was 64.57 months and OS was 66.81 months. There was no significant difference in survival between tumour subgroups.

Conclusions: We present OE cohort data demonstrating a diverse tumour cohort, with a dominant SCC group consistent with the literature. DFS and OS in our cohort demonstrate reasonable survival outcomes. Patients requiring OE may present with a diverse range of tumour types and histopathological characteristics, highlighting the complexity of the patient with orbital involving tumours.

Keywords: Orbital exenteration (OE); squamous cell carcinoma (SCC); carcinoma; cancer; orbit; peri-orbital

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Introduction

The surgical removal of orbital contents poses a significant challenge to the patient faced with a life-threatening peri-orbital or orbital malignancy. Orbital exenteration (OE), first described by Bartisch in 1583 (1), is the surgical removal of the orbit and its surrounding adnexa and is reserved for patients who have disease not amenable to eye preserving surgical intervention (2-4). It is important the surgeon performing OE understands the impact on survival,

and the cosmetic and functional challenges faced by the OE patient. Survival following OE has been investigated across a range of settings, however, varied survival statistics have been reported. Histopathological data has also been investigated in several cohorts, with diversity of tumour types and variation in tumour or pathological characteristics noted (5-14). A previous Australian cohort has demonstrated a predominance for SCC (14). Similar cohorts have been described in studies from other regions where chronic sun

exposure is common (7,9). In comparison, studies from other geographical regions with lower chronic sun exposure or lower exposure to ultraviolet light more commonly have cohorts in which basal cell carcinoma (BCC) forms the dominant tumour type (6,11,12). Despite varying dominant tumour types, the clear commonality between cohorts is a degree of heterogeneity in histopathology, with cohorts reporting up to 14 different tumour types identified (6,7,9-14). As such, survival outcomes can be difficult to predict in the context of small cohorts and tumour diversity. Furthermore, Patients face significant morbidity as a consequence of OE, with risk of adverse functional and cosmetic outcomes which can impact quality of life (15). OE is a significant life event for the patient and can result in poorer health-related and vision-related quality of life (15-18). Thus, it becomes important that patients are able to make an informed decision regarding OE and are able to develop reasonable expectations regarding the likely impact surgery will have on survival and quality of life. We present demographic, tumour and survival data of patients who have undergone OE at our centre between 2005 and 2015 and discuss the results in relation to the current literature.

Methods

Prior to commencing the study, ethics approval was granted by the Human Research and Ethics Committee of the local health district. A retrospective chart review of paper based and electronic medical records, imaging and histopathology reports, and existing head and neck databases was performed. Patients were included in the study if they had undergone OE between 1st of January 2005 and 31st of December 2015, were alive at time of exenteration (i.e., exenteration was not performed for organ donation) and were aged older than 16 years at time of exenteration. Patients were excluded if they did not meet the criteria above. Data collected included epidemiological data, disease specific and histopathological data, treatment modalities, surgical data (including number of procedures performed and surgical margins), recurrence status and vitality status at the study end points.

Disease free survival (DFS) and overall survival (OS)

DFS and OS was determined following review of existing databases, medical records and through liaison with the patients' general practitioner and treating specialists. Kaplan Meier analysis was performed to estimate DFS and OS using IBM SPSS Statistics (Version 25) software and

Kaplan Meier curves were generated. Subgroup analysis was performed of tumour subgroups to generate survival curves, and Log Rank analysis (Mantel Cox) was performed to determine significance between subgroups.

Results

Cohort data

A total of 35 orbits of 35 patients were included for statistical analysis (*Table 1*). There were 23 male and 12 female patients (male:female of 1.9:1). The median age at exenteration was 69.4 years old (range 32.1 to 91.4 years). Patients who underwent OE for squamous cell carcinoma (SCC) were older (median age 84.6 years) compared to those who underwent OE for BCC (68.7 years) or other tumours (59.1 years). Ten of 35 patients gave a history of smoking (28.6%), and all but two patients were independent in activities of daily living prior to exenteration. Exenteration was performed for recurrent tumours in 12 patients (28.6%): 7 in the SCC group, 3 in the BCC group and 2 in the other tumour types group (1 neuroblastoma and 1 melanoma). All patients except for two (one who died days after surgery, and the other was a palliative procedure in the setting of metastatic melanoma) received adjuvant radiotherapy. Additionally, 9 patients (25.7%) required secondary surgery following exenteration, with indications ranging from treatment of recurrence, to staged reconstruction and flap revision, to debridement and management of post-operative wound infection.

Histopathological diagnosis

There were ten different tumour types identified. Of note, 42.9% of the cohort who underwent OE had a confirmed diagnosis of SCC (15 patients). There were 6 patients with confirmed BCC (17.1%) and 14 patients who underwent OE for other tumour types: 3 adenoid cystic carcinoma, 2 sarcoma (1 rhabdomyosarcoma), 3 sinonasal undifferentiated carcinoma, 2 melanoma, 1 neuroblastoma, 1 small cell neuroendocrine carcinoma, 1 oncocytic carcinoma and 1 transitional cell carcinoma.

Surgical margins

Twelve patients (34.3%) had positive surgical margins and all but one (who died shortly after surgery) underwent adjuvant radiotherapy or chemo-radiotherapy. Three of these patients went on to develop recurrence (25%), three

Table 1 Patient cohort

No.	Histology	Subsites	Location	Performed in the setting of recurrence	Additional surgery	Clear margins	PER or LYM invasion	Recurrence (months)	Status at last follow up	Smoker	Sex
1	Neuroblastoma	Nil	Nasal/Ethmoid	Yes	No	Yes	LYM	Yes [9]	Deceased [12]	No	Male
2	Melanoma	Thoracic; hepatic	Choroid	Yes (palliative)	No	Yes	Nil	Metastatic at time of surgery	Deceased [5]	No	Male
3	Adenoid cystic carcinoma	Nil	Nasolacrimal	No	Yes (recurrence)	No	Nil	Yes [24]	Alive	No	Female
4	SCC	Parotid	Upper lid	No	No	Yes	Both	No	Deceased [13] (upper gastrointestinal bleed)	No	Male
5	Sarcoma	Nil	Posteromedial orbit	No	Yes (stage II OST)	Yes	PER	No	Alive	No	Male
6	RHA	Nil	Alveolar	NO	No	Yes	Nil	No	Alive	Yes	Male
7	SCC	Nil	Lateral canthus	No	No	Yes	Nil	No	Alive	Unclear	Male
8	BCC	Nil	Medial canthus	Unclear	Unclear	No	Nil	No	Lost to follow up	No	Female
9	SCC	Nil	Ethmoid	Yes	No	No	Nil	No	Lost to follow up	No	Female
10	BCC	Nil	Orbit/Peri-orbit	No	No	No	Nil	No	Deceased [34]	Yes	Male
11	Adenoid cystic carcinoma	Nil	Maxillary sinus	No	No	No	PER	No	Alive	Yes	Male
12	SCC	Nil	Ethmoid	Yes	No	No	LYM	No	Deceased [76]	No	Male
13	Sinonasal undifferentiated carcinoma	Nil	Maxilla	No	No	No	Nil	No	Deceased [26]	No	Female
14	SCC	Nil	Sinonasal	No	No	Yes	Nil	No	Alive	No	Male
15	BCC	Nil	Lower lid	Yes	No	No	Nil	No	Alive	Yes	Male
16	SCC	Nil	Upper lid	Yes	Yes	Yes	Nil	No	Alive	No	Female
17	SCC	Nil	Cheek	No	No	Yes	Nil	No	Alive	Yes	Male
18	SCC	Nil	Conjunctiva	Yes	No	Yes	Nil	Yes [22]	Deceased [34]	Yes	Male
19	Oncocytic carcinoma	Nil	Nasolacrimal/Orbit	Unclear	Yes	No	Both	Yes [5]	Deceased [41]	Unclear	Male
20	SCC	Nil	Maxillary sinus/lacrimal	Yes	No	Yes	Nil	No	Deceased [83] (Pneumonia)	No	Female
21	Adenoid cystic carcinoma	Nil	Nasolacrimal	No	Yes	Yes	Nil	No	Alive	No	Female
22	Transitional cell carcinoma	Nil	Nasal	No	No	Yes	Nil	No	Alive	No	Female
23	BCC	Nil	Medial canthus	No	No	Yes	Nil	No	Alive	Yes	Male

Table 1 (continued)

Table 1 (continued)

No.	Histology	Subsites	Location	Performed in the setting of recurrence	Additional surgery	Clear margins	PER or LYM invasion	Recurrence (months)	Status at last follow up	Smoker	Sex
24	SCC	Nil	Orbit	Yes	No	Yes	Nil	No	Alive	No	Male
25	SCC	Nil	Nasal	No	No	Yes	Nil	No	Alive	No	Male
26	SCC	Nil	Lateral canthus	No	No	Yes	Nil	No	Deceased [9]	No	Female
27	Melanoma	Nil	Nasal	No	No	Yes	Nil	Yes [60]	Deceased [64]	No	Male
28	SCC	Nil	Cheek	No	Yes	Yes	Nil	No	Alive	No	Male
29	SCC	Nil	Cheek	No	No	Yes	LYM	No	Alive	Yes	Female
30	Sinonasal undifferentiated carcinoma	Nil	Lacrimal	No	Yes	Yes	Nil	No	Alive	No	Female
31	Sinonasal undifferentiated carcinoma	Nil	Sinonasal	No	No	No	Nil	Yes [3]	Deceased [63]	Yes	Male
32	BCC	Nil	Nasal	Yes	No	Yes	PER	No	Alive	No	Female
33	Small cell neuroendocrine carcinoma	Nil	Ethmoid	No	Yes (EVD insertion)	No	Nil	No	Deceased (3 days)	Yes	Male
34	BCC	Nil	Cheek	Yes	No	Yes	Nil	Yes [51]	Alive	No	Male
35	SCC	Nil	Medial canthus	Yes	Yes	No	Nil	No	Deceased [7] (ischaemic colitis and sepsis)	No	Male

Patient cohort demonstrating cohort tumour diversity. SCC, squamous cell carcinoma; RHA, rhabdomyosarcoma; BCC, basal cell carcinoma; OST, osteointegration; EVD, external ventricular drain; PER, perineural; LYM, lymphovascular.

died from causes not related to their disease (one patient developed an intracranial haemorrhage shortly after surgery, one died 7 months after surgery from ischaemic colitis and sepsis, the third died from ischaemic heart disease), and four remained disease free during the study period. DFS of patients with involved surgical margins was 44.96 months (25.25 to 64.66 months), and OS was 54.67 months (36.05 to 73.29 months).

Perineural and lymphovascular invasion

On histopathological analysis, 5 patients (14.3%) exhibited perineural spread (2 with associated lymphovascular invasion) and 3 patients (8.6%) had lymphovascular invasion alone.

DFS

Seven patients had a confirmed recurrence of their disease. Of these, only one had involved surgical margins, all received radiotherapy or chemo-radiotherapy, and three patients had undergone OE in the setting of recurrence following prior surgical intervention of their tumour. Histopathology of the tumours that recurred included one patient with SCC, one with adenoid cystic carcinoma, one patient with neuroblastoma, one melanoma, one BCC and one undifferentiated carcinoma. Kaplan-Meier estimates of DFS revealed mean DFS of the cohort was 64.57 months (95% CI: 48.45 to 80.71 months) (*Figure 1*). Mean DFS of the tumour subgroups was 68.56 months (95% CI:

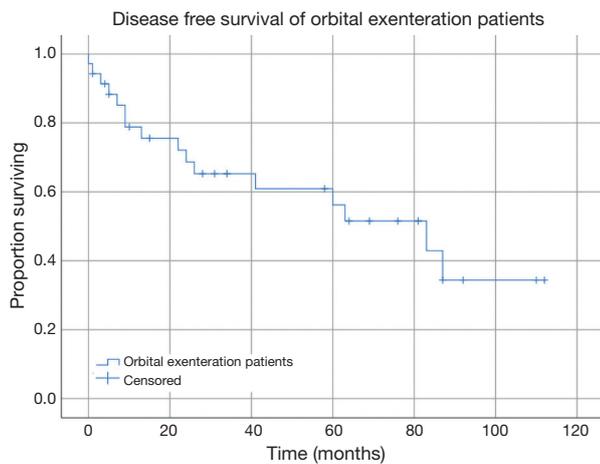


Figure 1 Disease free survival (DFS) of cohort. Mean DFS of all patients undergoing OE in this cohort was 64.57 months (95% CI: 48.45 to 80.71). OE, orbital exenteration.

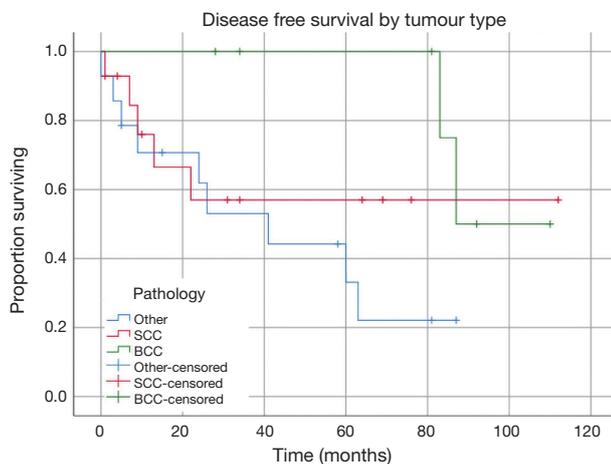


Figure 2 Disease free survival (DFS) of tumour subgroups. Mean DFS of the tumour subgroups was 68.56 months (95% CI: 39.39 to 97.74) for the SCC group, 97.50 months (95% CI: 85.17 to 109.83) in the BCC group, and 42.14 months (95% CI: 24.47 to 59.80) in the other tumour group. There was no statistically significant difference between tumour subgroups ($P=0.099$). SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

39.39 to 97.74 months) for the SCC group, 97.50 months (95% CI: 85.17 to 109.83 months) in the BCC group, and 42.14 months (95% CI: 24.47 to 59.80 months) in the other tumour group (Figure 2). There was no statistically significant difference between tumour subgroups ($P=0.099$).

OS

Kaplan Meier estimates of OS revealed mean survival for the cohort was 66.81 months (95% CI: 51.56 to 82.06 months) (Figure 3). This included all causes of death. Patients who had a confirmed SCC requiring exenteration had a mean OS of 68.46 months (95% CI: 39.35 to 97.59 months), in comparison the 97.50 months (95% CI: 85.17 to 109.83 months) for the BCC group and 49.07 months (95% CI: 33.11 to 65.02 months) for the other tumour group (Figure 4). There was no statistically significant difference between survival for tumour subgroups ($P=0.131$).

Discussion

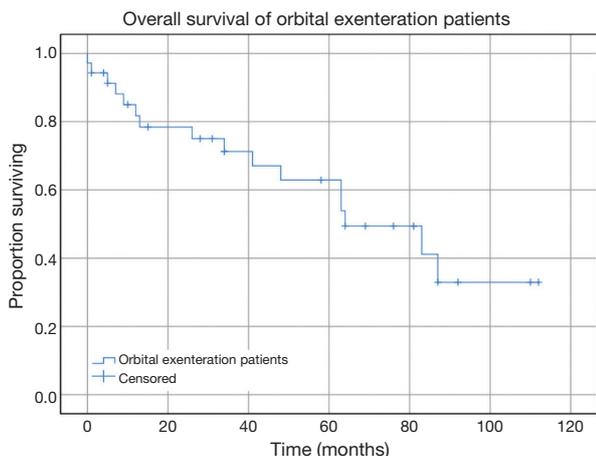
OE is a highly invasive surgical procedure with cosmetic and functional consequences that can adversely impact quality of life. In the setting of malignancy, exenteration is performed for patients who have life threatening disease not amenable to less invasive surgical procedures.

Survival

There have been several studies investigating the survival of OE patients across a range of centres. In our cohort, we report DFS of 64.57 months and OS of 66.81 months, which is comparable to other similar size studies and similar cohorts. Aryasit *et al.* reported OS of 46.68 months (3.89 years) and event free survival (EFS) of 36.12 months (3.01 years) in 39 patients who underwent OE for malignancy (9). Hoffman *et al.* in a study of 31 consecutive patients undergoing OE over a period of 7 years reported OS of 78.4 months (14). Other studies have reported 48–67% three-year survival and 37–68.3% survival at 5 years (7,12,13). Wu *et al.*, in a study of 24 patients who underwent OE in the setting of invasive maxillary sinus SCC reported 5-year survival 27.3% (19). Ten-year survival of 37% was reported in one study (12). DFS is equally diverse in the literature. Gerring *et al.* reported DFS in a cohort of 49 patients who underwent OE for BCC, SCC and sebaceous gland carcinoma (DFS 52.6, 39.2 and 28.1 months respectively) (8). Roche *et al.* reported recurrence of 36% in 22 patients (20). Our recurrence rate in comparison was 25.7%.

Tumour histology

The tumour histopathology of patients undergoing OE



has historically been diverse. In our cohort, we divided **Figure 3** Overall survival (OS) of cohort. Mean survival for the cohort was 66.81 months (95% CI: 51.56 to 82.06 months).

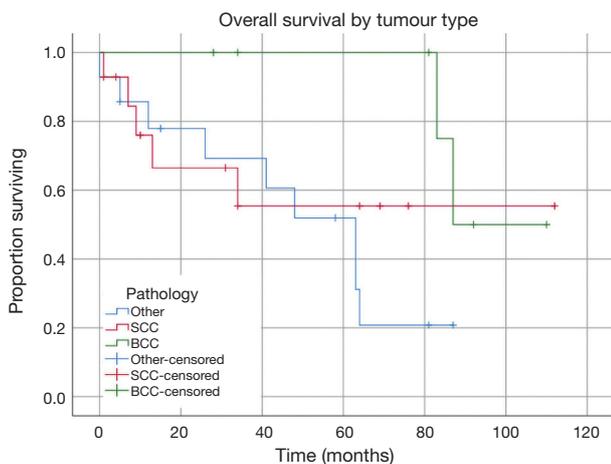


Figure 4 Overall survival (OS) of tumour subgroups. Mean OS of SCC patients was 68.46 months (95% CI: 39.35 to 97.59 months), BCC patients was 97.50 months (95% CI: 85.17 to 109.83 months) and patients with other tumour types was 49.07 months (95% CI: 33.11 to 65.02 months). There was no statistically significant difference between survival for tumour subgroups (P=0.131). SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

our patients into three subgroups: SCC, BCC and other tumour types based on the frequency of tumour types. There were in total 10 different tumour types. SCC was the most common (15 patients) followed by BCC (6 patients). The tumour histopathology in our cohort is similar to the numbers reported by Hoffman *et al.* who reported 15 cases of SCC, 8 BCC and 8 other tumour types in a cohort of 31

patients undergoing OE in a similar setting (14). Mouriaux *et al.* (7) and Aryasit *et al.* (9) also published a similar case mix to ours. Ben Simon *et al.* in a cohort of 34 patients reported SCC as the dominant tumour type, followed by BCC and melanoma (21). The authors suggested that a predominance of SCC in their cohort may be attributed to high index of suspicion for BCCs and early intervention. Other centres have reported higher rates of BCC than SCC in their patient cohorts. Rahman *et al.* 2005 reported 28 cases of BCC leading to OE in a cohort of 68 (compared with 6 cases of SCC) (6) and Wong *et al.* in a cohort of 73 patients reported 27 BCC and 14 SCC (11). Similarly, Rathbun *et al.* described 14 cases of BCC in a cohort of 48, and 6 cases of BCC (22), and Nassab *et al.* reported 17 cases of BCC in 32 patients undergoing OE (4). The most consistent feature amongst cohorts is significant tumour histological diversity, with studies reporting up to 14 tumour types described as indications for OE (9). Our cohort supports the complexity of tumour histopathology in patients undergoing OE.

Perineural and lymphovascular invasion

Perineural invasion (PNI) is considered an important prognostic factor for malignancies involving the orbit. Peri-orbital SCC in particular, has demonstrated PNI in a significant proportion of patients undergoing surgical resection, with time to treatment an important factor for reducing orbital invasion and PNI (23). In patients with SCC, PNI and lymphovascular invasion are both associated with increased risk of metastases and death from disease (24). Adenoid cystic carcinoma is also associated with a particularly poor prognosis due to its protracted course, and high rates of PNI (25). In our cohort 5 patients exhibited PNI with or without lymphovascular invasion: adenoid cystic carcinoma (1 of 3 patients with this pathology), SCC, BCC, sarcoma and oncocytic carcinoma. Subgroup survival analysis was not performed in the setting of small numbers of patients with PNI and lymphovascular invasion.

Involved surgical margins

Involvement of surgical margins in our cohort was demonstrated in 12 of 35 patients (34.8%). This is in keeping with other cohorts which report involved margins in 22–52% of patients (8,12,13). The impact of involved surgical margins has been evaluated in a range of studies in the literature. The current literature demonstrates that

involved surgical margins do not appear to impact OS but are associated with increased risk of local recurrence. In our cohort, of those with involved surgical margins, 25% had local recurrence of their disease, and those with recurrence had a lower DFS and OS relative to the rest of the cohort. Rahman *et al.* (12) found there was no statistically significant difference in 3-year survival ($P=0.99$) in patients with involved versus clear surgical margins in a cohort of 64 patients (34 patients with clear margins and 30 with involved margins). Additionally, they demonstrated that patients with clear surgical margins had a 5-year survival of 53% compared with 63% in the involved surgical margins which was not statistically significant ($P=0.454$). Subgroup analysis did not show any statistically significant survival differences when assessing surgical margins in tumour subgroups in their study (12). Similarly, Nagendran *et al.* (13) showed no difference in survival in clear versus involved margins ($P=0.12$). Aryasit *et al.* (9) analysed the survival of patients in a cohort of 39, comparing those with involved surgical margins with those who were clear. There was no significant difference in OS demonstrated in this cohort ($P=0.597$), however the authors noted that a high proportion of patients within the group who had involved surgical margins also had high rates of nodal or distant metastases at time of diagnosis. Similarly, Mouriaux *et al.* (7) demonstrated no significant difference in OS in patients with involved versus clear surgical margins ($P=0.13$). They did demonstrate, however, that clear surgical margins significantly improved rates of local recurrence ($P=0.01$). In comparison, Gerring *et al.* (8) demonstrated involved surgical margins were associated with poorer prognosis in patients with non-melanoma skin cancers who underwent OE. Of 49 patients studied in this cohort, 11 patients (5 BCC and 6 SCC) had positive surgical margins. Multivariate analysis demonstrated that involved surgical margins were a predictor of poorer prognosis ($P=0.002$, 95% CI: 2.73–102.11). The authors identify that the results may be attributed to sample size, and comparisons may be difficult due to heterogeneity of inclusion criteria across studies.

Conclusions

OE is reserved for patients with life threatening peri-orbital or orbital malignancy for whom less invasive surgical procedures would not be adequate. We report our data of patients who have undergone OE at our centre, with reasonable survival outcomes. The tumour histology in our

cohort is diverse, which is consistent with the literature. The significant morbidity associated with OE, and risk of recurrence following surgery highlights the importance of informed consent and discussion about likely survival and quality of life following surgery.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/ajo.2019.09.03>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Prior to commencing the study, ethics approval was granted by the Human Research and Ethics Committee of the local health district. Informed consent was waived due to the retrospective nature of the study.

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