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Low recurrence of lung adenoid cystic carcinoma with radiotherapy and resection

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Abstract

Introduction:

Adenoid cystic carcinoma (ACC) is a rare cause of thoracic malignancy and the prognosis may depend on extent of surgical resection and adjuvant radiotherapy. Complete resection has low rates of local recurrence but is complicated by the involvement of central airways. Adjuvant radiotherapy is frequently recommended, but unproven.

Aims

We describe the technicalities of radical resection and adjuvant radiotherapy, using the primary endpoint of local recurrence and secondary endpoints of locoregional (mediastinal) recurrence and distant metastasis. Resections were classed as microscopically and macroscopically clear (R0) or only macroscopically clear (R1).

Results

12 patients (8 male) diagnosed between 1999 and 2016, at an average of 44 ± 12 years. Six of these were operable (operative group), and six had non resectable lesions (radiotherapy group).

In the operative group, three had tracheal disease and three had bronchial disease. Tracheal lesions underwent excision with tracheal anastomosis (all R1 resections). Main bronchial lesions underwent complete excision via pneumonectomy (Two R0 and one R1 resection). All these patients received 50-60 Gy of adjuvant radiotherapy. At an average follow up was 6.1 ± 4.3 years, no patients had local recurrence, two had locoregional recurrence and four had distant metastasis. The radiotherapy group received 60-70 Gy as definitive therapy and at an average follow up was 5.4 ± 4.2 years, three had locoregional recurrence, four had distant metastasis.

Conclusion

Our case series consolidates evidence that early radical resection and radiotherapy is associated with a low risk of local recurrence in patients with thoracic ACC.

Introduction

Adenoid cystic carcinoma (ACC) is a rare cause of thoracic malignancy, more commonly being associated with salivary glands in the head and neck. As a result, there is a paucity of data from multicentre trials with treatment being unproven and fraught with uncertainty [1-14].

The natural history and prognosis are highly variable, but may depend on the extent of surgical resection and adjuvant radiotherapy. In the largest case series to date, the 5 and 10 year mortality has been reported from 65-97.6% and 53.0-86.7% respectively [5, 10].

Complete resection (R0), where possible, has low rates of local recurrence (0%-7.6%), but in the thorax, this is complicated by the involvement of the central airways, including the trachea, bronchus and rarely lung parenchyma. This renders surgical resection difficult and often incomplete due to risk of functional limitations, poor anastomosis on resection and poor operative access. Bronchoscopic interventions can be used to relieve airway pressure and to achieve tissue diagnosis.

Adjuvant radiotherapy is frequently recommended, but this practice is unproven and there is a lack of consensus on its effectiveness. No clinical trials have established a role for adjuvant chemotherapy to date [1, 5, 9-11].

Our centre has had no local recurrence and no mortality at an average follow up of 6.1 years. We present this case series to advocate for radical surgical resection and adjuvant radiotherapy for thoracic ACC.

Aims

We aim to describe the technical aspects of early radical resection and adjuvant radiotherapy, using the primary endpoint of local recurrence at the excision site and secondary endpoints of locoregional (mediastinal) recurrence and distant metastasis.

Methods

Ethics approval was obtained from the local hospital ethics committee (Peter MacCullum Cancer Centre). Medical records were accessed in retrospect to analyse all cases of thoracic ACCC between 1999-2016 at the Royal Melbourne Hospital and VCCC.

Local recurrence was defined as any disease recurrence at the excision or target radiotherapy site, Locoregional recurrence was defined as any mediastinal recurrence and distant metastasis was defined as metastasis outside the mediastinum. Extent of resection was classified as R0 (complete excision with both macroscopically and microscopically clear margins), R1 (macroscopically clear margins only) or R2 (no clear margins, macroscopically or microscopically).

Data was compiled and analysed using Microsoft Excel (2013).

Results

Demographics

There were 12 patients (8 male) with Adenoid Cystic Carcinoma diagnosed between 1999 and 2016 with an average age at diagnosis of 44 years \pm 12 years. All patients were diagnosed with functional imaging (CT, PET) and tissue biopsies (EBUS or CT guided), and discussed at multidisciplinary meetings (MDM) regarding treatment modality.

Six patients were deemed operable with intention for complete resection and classified as the operative group. The remaining 6 patients had non resectable lesions with locoregional invasion, and

were classified as the radiotherapy group (Figure 1). Half of this group (n=3) had distant metastasis at the time of diagnosis.

Operative Group

In the operative group (n=6), three had tracheal disease and three had bronchial disease (Table 1). Patients with main bronchial disease underwent complete surgical excision via pneumonectomy (n=3) (Figure 2), of which two were R0 and one was R1. Patients with tracheal disease underwent tracheal excision with tracheal anastomosis, all of which were R1 (Figure 3). One of these patients also underwent endobronchial excision. Reasons for incomplete R1 resections were inability to safely resect all tumour mass without disrupting the trachea (n=4), lung hilum (n=1) or main bronchus (n=1).

Radiotherapy

Patients in the Radiotherapy group were administered 60-70 Gy of radiation at 2 Gray (Gy) per fraction over 40-50 days (Figure 4). This was targeted to the primary lesion (Figure 5a). All patients in the Operative Group received adjuvant radiotherapy of 50-60 Gy, at 2 Gy over 40-50 days to either the stump site or trachea (Figure 4 and Figure 5b).

Follow up

In the surgery group, the average follow-up was 6.1 ± 4.3 years (Range 3 – 16 years) (Figure 5). Survival free from locoregional recurrence was 100% (n=6/6) at 1 years, 60% (n=3/5) at 5 years and 33% (n=1/3) at 10 years. Survival free from metastasis was 100% (n=6/6) at 1 year, 80% (n=4/5) at 5 years and 33% (n=1/3) at 10 years. All patients who had metastasis had locoregional recurrence, and the sites of metastasis included the spleen, muscle, liver and right clavicle.

In the radiotherapy group, the average follow-up was 5.4 ± 4.2 years (Range 1-11 years) (Figure 5). All had invasive locoregional disease at diagnosis, and three had metastasis. Of the non-metastatic patients (n=3), survival free from metastasis was 33% (n=1/3) at 1 year, and 0% (n = 0/2) at 5 years.

There was one mortality from both groups; this was a patient from the operative group, who underwent an R1 resection for a tracheal lesion, developed metastatic disease six years post operatively and died eleven years post diagnosis.

Discussion

Our experience is that thoracic adenoid cystic carcinoma is a malignancy of young, otherwise well patients (average age at diagnosis: 44 years \pm 12 years), with no predilection towards sex or lifestyle factors such as smoking. It has an indolent progressive course which is commonly misdiagnosed due to non-specific symptoms such as shortness of breath, non-productive cough, hoarseness, chest pain or loss of weight.

Our centre advocates for early radical resection with adjuvant radiotherapy after discussion in a multi-disciplinary team setting. Evidence for this strategy is scant and based on the experience of ACC in the head and neck. The largest series for thoracic ACC did not administer radiotherapy to all patients, and was characterised by recurrence, with a median disease free survival (DFS) of 10.2 years and 5-, 10-, 15- and 20-year disease-free survival rates at 67%, 53%, 38% and 26%, respectively [10[15]]. Even though the majority of patients in the operative group had incomplete resections (R1), there was no recurrence or mortality at an average follow up of 6.1 years; a novel finding which has not been achieved to date, which we believe may be attributable to operative resection of tumour mass, even if incomplete, with early radiotherapy.

This case series also highlights the difficulty in achieving clear resection margins due to several reasons. Firstly, half of our patients had disease in a region where it was surgically inaccessible, or risked significant functional compromise, therefore making these patients inoperable. Amongst the operative candidates (50%, n=6), resection margins had to be balanced with requirements for adequate anastomosis and restricting damage to surrounding structures. As a result, R0 resection was not possible in any patient with tracheal disease, and in only two of the three patients with bronchial disease despite undergoing pneumonectomies. This highlights the difficulty of operative intervention,

where resection is often more technically challenging than it initially appears. Furthermore, if the majority of patients receive R1 resections (n=4), it casts doubt over the benefit of any operative intervention, especially as these procedures are often very invasive and not free from morbidity. Furthermore, due to the mucosal and submucosal spread of this tumour it was difficult to identify clear margins macroscopically which suggests intraoperative frozen sections need to be taken to delineate margins, but this strategy for thoracic ACC is unproven. Overall, our rates of complete resection (16.7%, 2/12 patients) is in keeping with rates of clear margins from the literature of 9.1 – 37% [15] and further verifies reports citing the operative difficulty of achieving R0 resections.

Symptomatic endo-bronchoscopic measures are emerging as novel techniques for symptomatic relief; we only had one patient with such intervention, and cannot provide any evidence contraindicating its use.

There are case series starting to emerge which show that radiotherapy with an R1 resection can obtain long-term survival times equivalent to that found in patients with a negative margin resection (R0 resection) [2, 9-11, 15-24]. Our case series is supportive of these findings; survival free from metastasis in patients who underwent R0 resection was 50% (n=1/2) at 5 years and 0% (n=0/2) at 10 years, compared to 0% (n=0/3) at 5 years and 10 years for patients who had incomplete resections. However larger case series are required to further consolidate its role in clinical practice.

This case series is promising as it confirms the role of radical resection and adjuvant radiotherapy as a means of achieving freedom from local recurrence. If this is attainable, and the disease is truly spread mucosally and submucosally via a haematogenous route, then it provides a method for local clearance to prevent further spread. However, this study, like many others to date, are marred by lack of a large patient population required to obtain statistical significance. Large multicentre studies over several decades, especially with adjuvant radiotherapy, are required to investigate treatment options further.

Furthermore, whilst this case series reports no mortality, metastasis still did occur, raising the possibility that ACC is spread via non-haematogenous routes, or that it presents late clinically when underlying metastasis has already occurred.

Conclusion

Our case series consolidates evidence that early radical resection and radiotherapy is associated with a low risk of local recurrence in patients with thoracic ACC.

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Tables

Pt No	Location of Tumour	Extent of Resection	Resection Method
1	Left Main Bronchus	R1	Left Pneumonectomy
2	Left Upper Lobe Bronchus and Left Main Bronchus	R0	Left Pneumonectomy
3	Right Main Bronchus	R0	Right Pneumonectomy
4	Distal Trachea and Right Main	R1	Elliptical excision of tumour over

	Bronchus		lateral wall of trachea extending over right main bronchus with anastomosis
5	Intratracheal, (2cm), 4.5cm proximal to the carina	R1	Endobronchial excision then Tracheal resection with anastomosis.
6	Tracheal	R1	Tracheal Resection with anastomosis

Table 1 – Operative details for patients with Thoracic ACC. Highlighted in yellow: Patients with disease in the main bronchus, requiring pneumonectomy. Highlighted in blue: Patients with disease in the trachea, requiring tracheal resections.

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Figure 2 – Typical imaging for bronchial disease: in this patient, a lesion is visible in the left upper lobe and left main bronchus, and underwent a pneumonectomy.

Figure 3 – Typical imaging for tracheal disease; in this patient, the lesion is intraluminal in the trachea, and this patient underwent a tracheal resection.

Figure 4 – Radiotherapy doses administered at 2 Gy per fraction to both the Radiotherapy and Operative (labelled Surgery + Adjuvant Radiotherapy) groups.

Figure 5 – The recurrence patterns for thoracic ACC in both operative and radiotherapy groups, divided by the local recurrence and locoregional and distant metastasis.

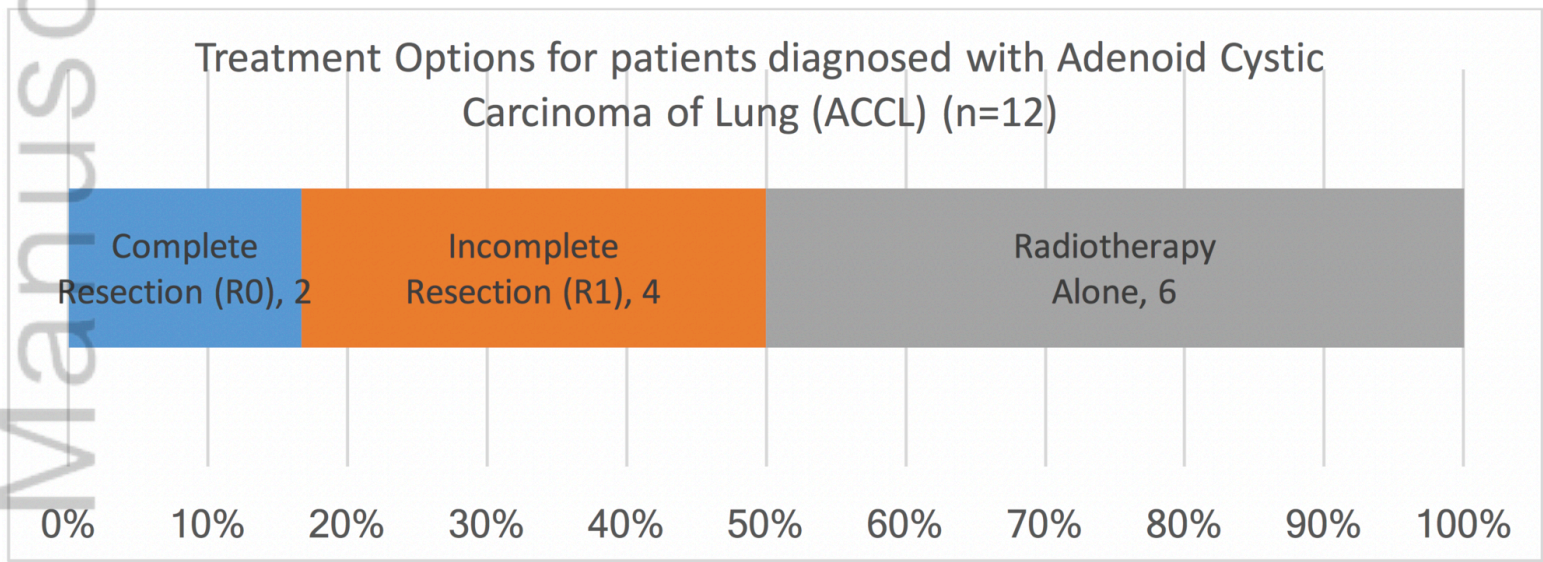


Figure 1 – The treatment modalities for the patients diagnosed with thoracic adenoid cystic carcinoma.

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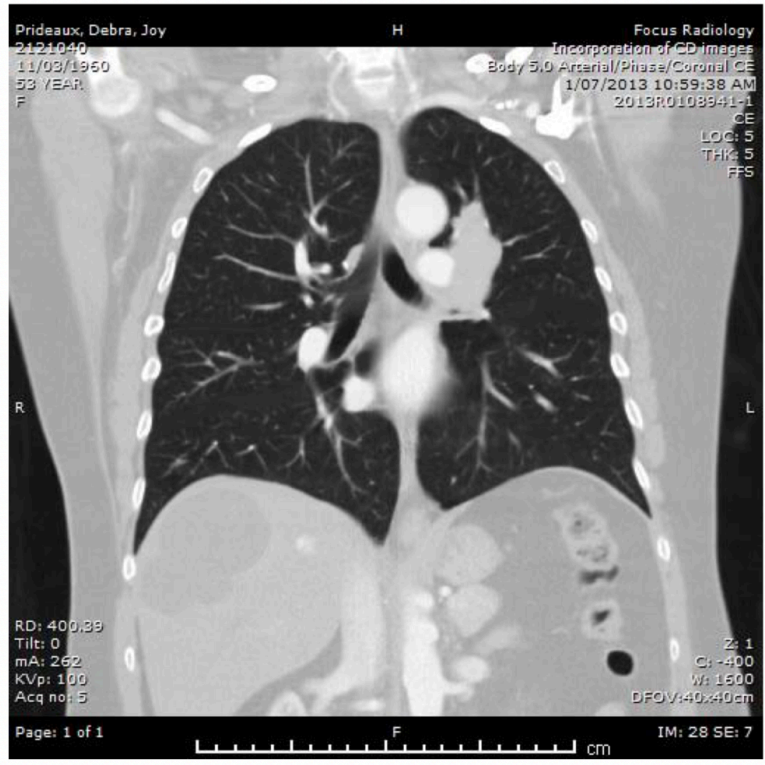
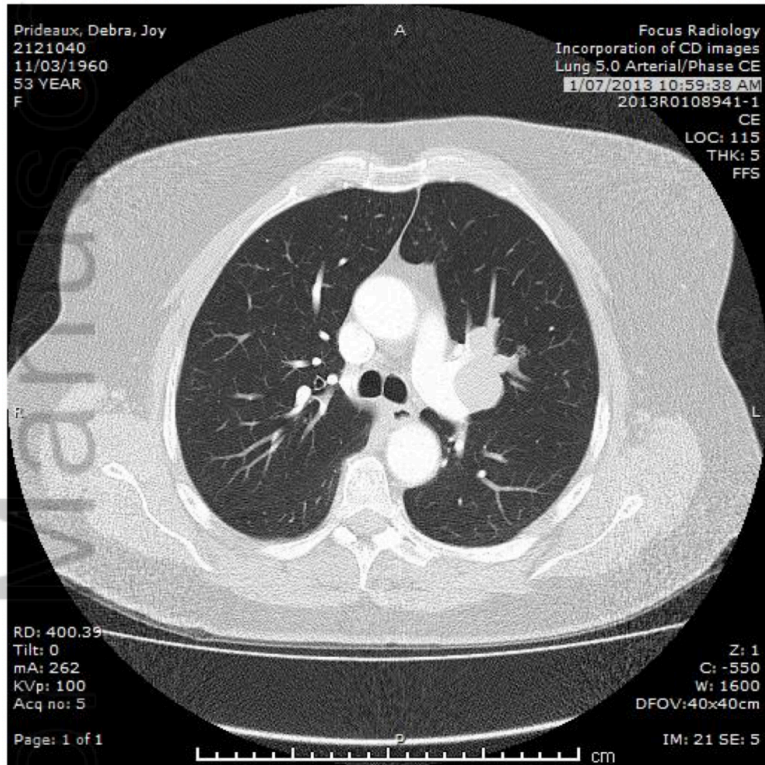


Figure 2 – Typical imaging for bronchial disease: in this patient, a lesion is visible in the left upper lobe and left main bronchus, and underwent a pneumonectomy.

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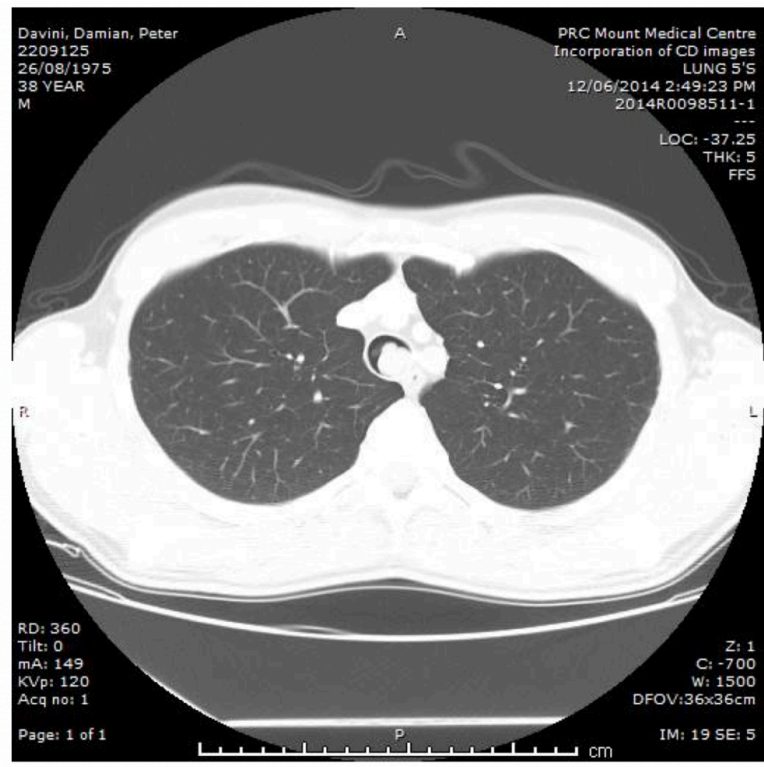
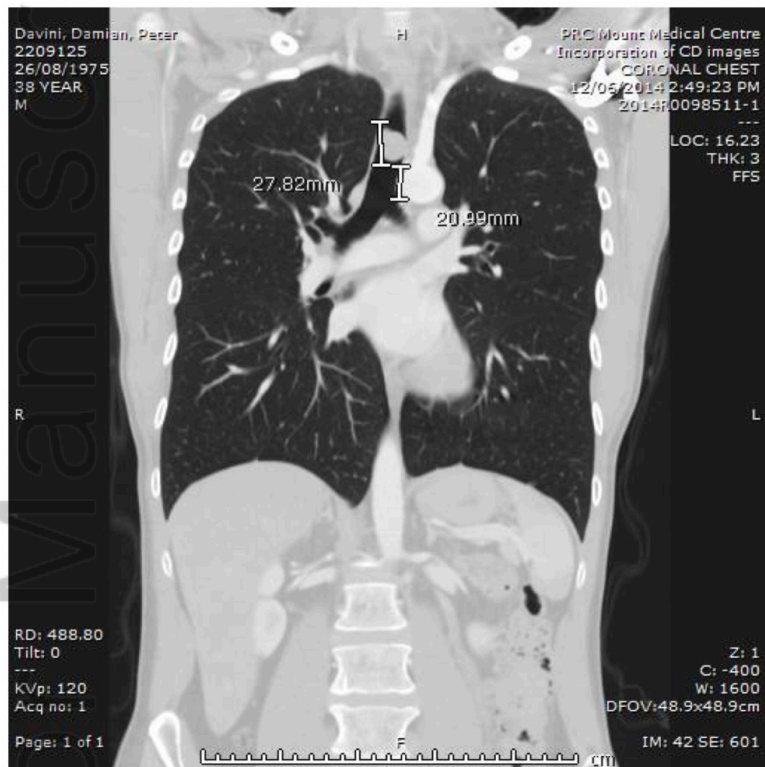


Figure 3 – Typical imaging for tracheal disease; in this patient, the lesion is intraluminal in the trachea, and this patient underwent a tracheal resection.

ANS_15222_Figure 3.tiff

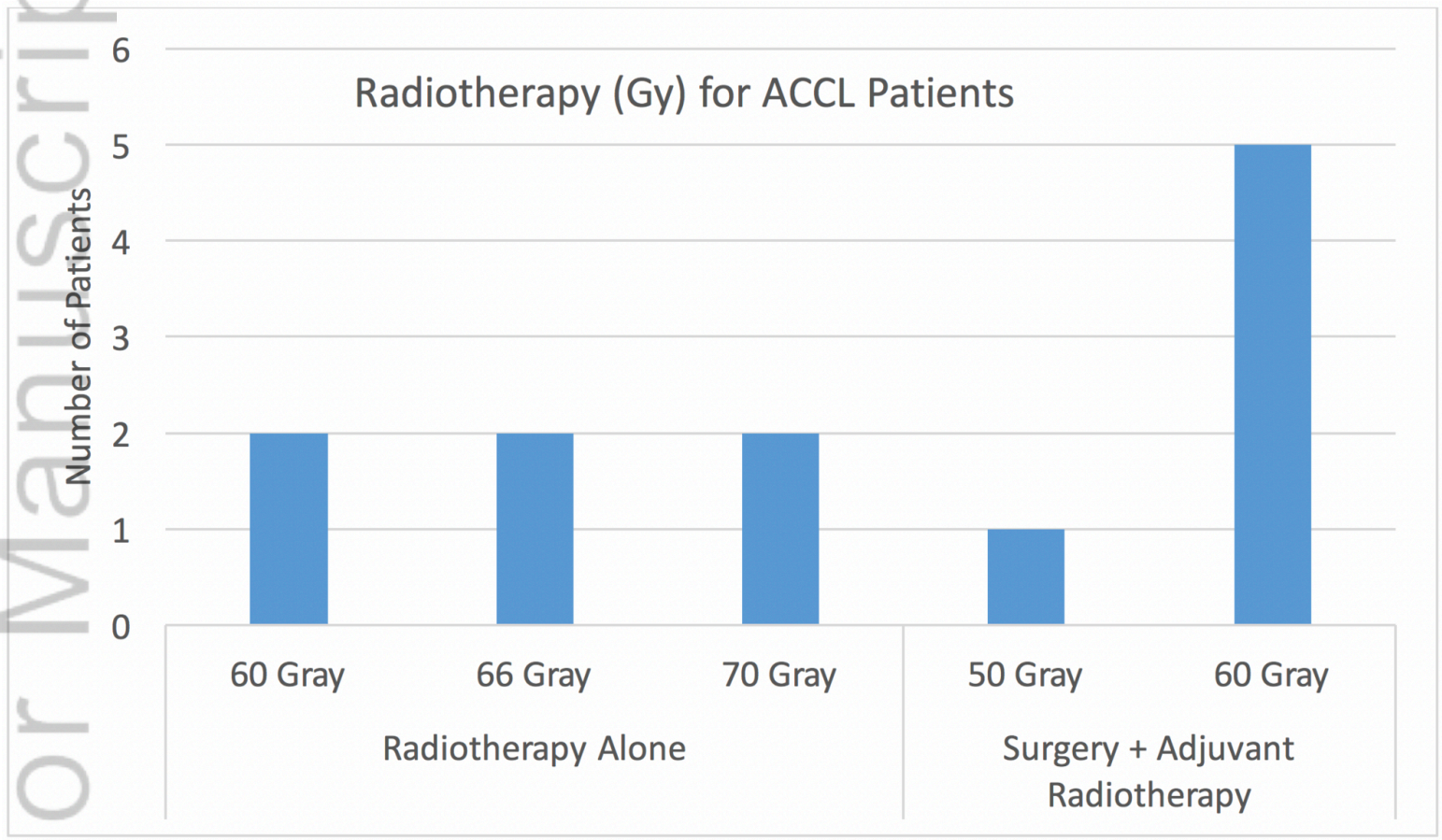
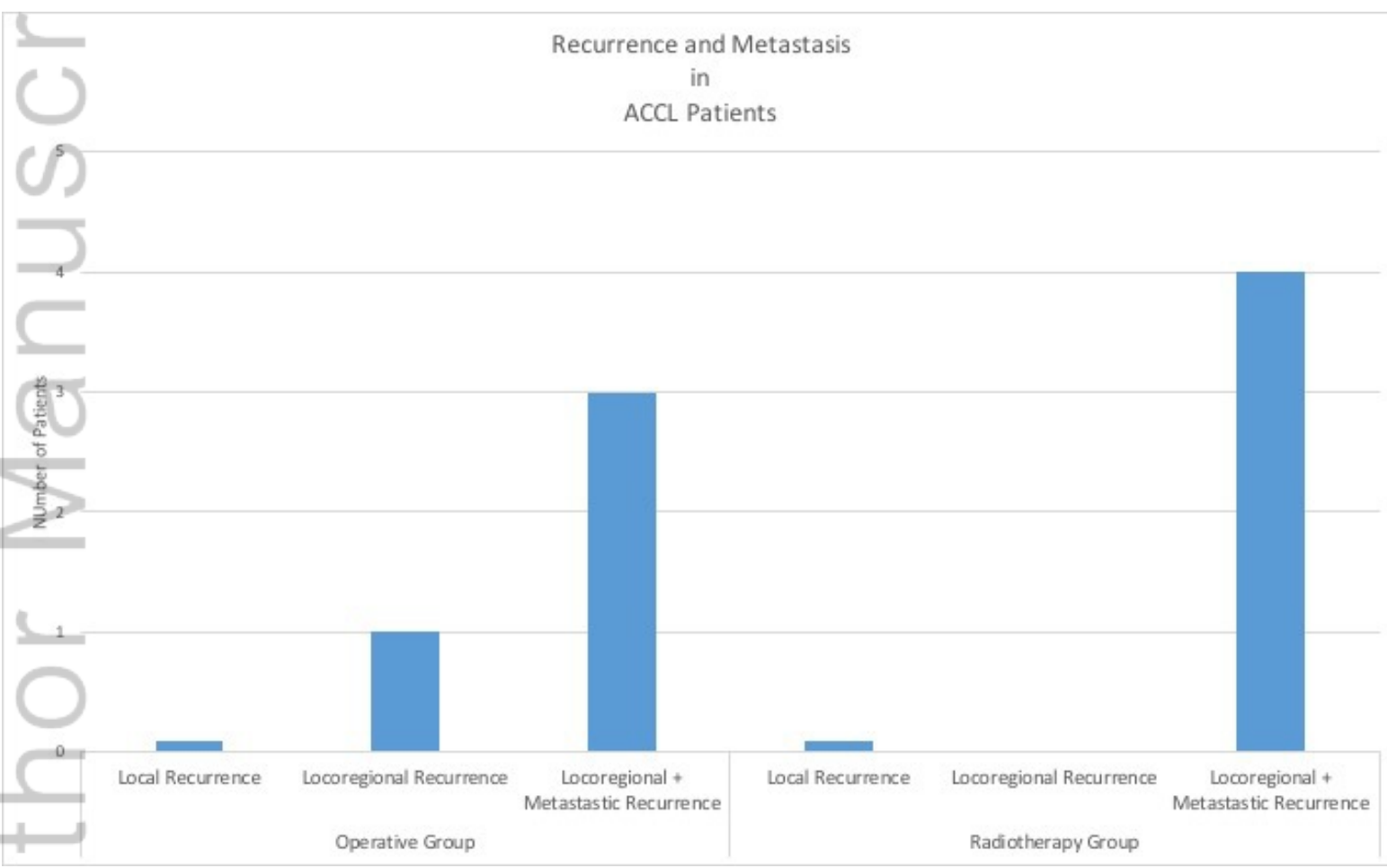


Figure 4 – Radiotherapy doses administered at 2 Gy per fraction to both the Radiotherapy and Operative (labelled Surgery + Adjuvant Radiotherapy) groups.

ANS_15222_Figure 4.tiff



ANS_15222_Figure 5.jpg