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Comparison of Radiology and Histopathology in Thymic Epithelial Tumours

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Abstract: Tumours of the thymus gland have a limited evidence base due to their low incidence rate. The Masaoka-Koga staging system has been known as the strongest prognostic indicator for both survival and recurrence of thymic tumours but there is no standardised way to assess clinical staging in pre-operative images. As appropriate staging can influence patients' need for adjuvant therapy, it is important to evaluate if current imaging can accurately predict post-operative staging. This was a retrospective study comparing the pre-operative radiological staging and post-operative pathological staging of 34 patients. This was conducted at the Golden Jubilee National Hospital between March 2013 and October 2016. A Kappa statistic was used to evaluate agreement between the assessments. 61.8% (21 out of 34) of the CT stages agreed with the pathology stages: 78.6% (11 out of 14) in stage I; 41.7% (5 out of 12) in stage II; 40% (2 out of 5) in stage III; and 100% (3 out of 3) in stage IV. There was moderate agreement between the preoperative CT assessment and the post-operative pathological staging (kappa coefficient = 0.42, p value < 0.01). With further analysis of a larger sample size it could be concluded that radiological staging of thymic tumours before surgery is quite accurate but requires standardisation and utilisation of other imaging techniques to ensure appropriate levels of care.

Keywords: Thymoma, Masaoka-Koga Staging, Histopathology

1. Introduction

Thymic epithelial tumour (TET) is a rare tumour developed from the thymus gland. With reported incidence rates of 1-5 people per million population developing a thymic epithelial tumour, researchers and clinicians have a very small evidence base for treating these patients [1] As such, a standard for histological classification of resected thymic epithelial tumours has been developed but a framework for the pre-operative radiological staging has not been universally accepted. The aim of this project is to compare the pre-surgery and post-surgery staging of thymic epithelial tumours and to assess any impact this may have on treatment plans.

The thymus gland is a bilobed mass of lymphoid tissue lying anterior to the trachea and retrosternally in the mediastinum. It has a relatively large size at birth but begins to diminish from puberty onwards as the cortex becomes infiltrated with fat. The thymus is the site of T lymphocyte maturation and proliferation, T cell regulating hormone secretion and apoptosis of self-reactant T cells. A fibrous capsule surrounds and separates the two lobes with its trabeculae penetrating and forming lobules. The outer cortex has many T cells while Hassall's corpuscles in the inner medulla serve as the site of auto-reactant T cell death.

The thymus pathology this project focusses on is tumours of the thymus epithelium. The majority of these are slow growing thymomas but some are found to be highly invasive thymic carcinomas. The causes of thymic epithelial tumours are unknown as there seems to be no correlation with usual predictors of cancer apart from genetic factors. Although there is no familial clustering of cases, there appears to be increased incidence in Asian/Pacific Island populations [2]. With thymic epithelial tumours accounting for half of anterior mediastinal masses

[3], patients with disease advanced enough to be symptomatic present with complaints relating to structures in the neck and chest. These include: persistent coughing; chest pain; upper airway congestion and difficulty swallowing. In severe cases, there may be obstruction of the superior vena cava leading to facial and arm swelling and reduction in cardiac return. The autoimmune neuromuscular condition myasthenia gravis has a well-documented association with thymic epithelial tumours as approximately a third of patients with TETs will have myasthenia gravis [3]. Removing the neoplastic thymus gland is done in the hope to reduce symptoms of myasthenia gravis. There are several other autoimmune conditions associated with thymic epithelial tumours such as pure red cell aplasia and gammaglobulin deficiency occurring in 2-5% of thymic tumour patients. Other malignancies are often found in patients before or after their thymoma and, as the thymus is a primary lymphoid organ, this is thought to be caused by decreased immune competency [4]. Thymic epithelial tumours are diagnosed from any apparent clinical symptoms and their appearance on radiological scans. They are only confirmed once surgically excised at histopathology.

The primary treatment for a thymic epithelial tumour is surgical excision either through the sternum or the chest wall (with the assistance of cameras). If the surgery is not deemed enough to completely remove the chance of recurrence, the patient may undergo radiotherapy or chemotherapy. This is termed adjuvant therapy. They may also receive this before an operation (when it is called neo-adjuvant therapy) in a bid to downstage or shrink the tumour.

The widely accepted Masaoka-Koga staging system [5] - modified from the Masaoka system [6] – is based on survival statistics and used to histologically assess thymic epithelial tumours. Assessing tumours with staging classifications can allow more accurate prognostic predictions to inform patients and doctors but the information can also be used to fuel decisions on treatment. Stage I tumours are contained within the capsule surrounding them with no abutment of the great vessels. Stage II tumours show some invasion out with this capsule and into the surrounding fatty tissue. There is a subdivision of stage II into A (microscopic capsular invasion) and B (macroscopic capsular invasion). Stage III tumours have invasion into neighbouring organs such as the pericardium, great vessels or the lungs. Stage IV tumours are recognised as having travelled beyond the original site of growth and deposited elsewhere. In the A substage this can be in nearby structures such as the pleura round the lungs and IVB tumours show more distant spread throughout the body via the blood or lymphatics. The 10- and 15- year survival rates found in a cohort of 307 patients who underwent thymectomy for stage I was 80% and 78% respectively; 78% and 73% for stage II; 47% and 30% for stage III and 30% and 8% for stage IV [7]. With regards to treatment decisions, the key differentiation is between stage II and III as best evidence shows that adjuvant chemotherapy or radiotherapy should be considered in patients with stage III and IV [8], [9].

The World Health Organisation (WHO) has laid out guidelines to classify the histological grade of thymic epithelial tumours. The grade identifies the cell types contained within a tumour and as the grades progress; increased malignant potential is found. Although little correlation has been found between the Masaoka-Koga stage of thymic epithelial tumours and their histological grade, it is important to appreciate grading [10]. Thymic tumours exhibiting little invasiveness may end up containing cells with a very malignant nature. The WHO classification for thymic epithelial tumours is as follows: type A contain spindle cells and are described as medullary in nature: type AB is mixed; type B1 is lymphocyte rich; type B2 is described as cortical; type B3 is a well differentiated thymic carcinoma and; type C is a heterogeneous thymic carcinoma [1].

The aim of this project is to evaluate the level of agreement between pre-operative staging, using radiological computed tomography (CT) scans, and the post-operative Masaoka-Koga histopathological staging. If clinicians can be confident in the stage of a tumour, they will not have to wait until the growth has been removed before making an effective decision on patients' treatment. This is a retrospective study using skills in interpreting anatomy in radiological scans and pathological reports.

Problems anticipated when undertaking this project include the retrospective nature not allowing standardised reporting techniques or consistent initial reporters. The IIA and IIB substage will not be fully compared between radiology and pathology as the CT scans cannot discern the microscopic invasion found in stage II.

2. Materials

34 anonymised patients were selected for this project. 14 were female and 20 were male with an age range of 27-82 (mean 62 years of age). These patients all received a thymectomy to remove an enlarged thymus gland between March 2012 and October 2016 at the Golden Jubilee National Hospital in Clydebank. 18 out of 34 (53%) of the patients were positive for myasthenia gravis while 7 (21%) had a history of other growths in the body. These tumours were transitional cell bladder carcinoma, breast cancer, renal cancer, follicular thyroid carcinoma, seminoma and the benign haemangioblastoma. 3 (9%) of the patients had other autoimmune conditions which were hypothyroidism and thyroid goitre. See Table 1 for a description of characteristics. Table 2 depicts the frequency of the WHO histological types.

Table 1. *Shows the characteristics of the patient sample.*

Characteristics	Value
Age (years)	27-82 (mean 62)
Male/female	20 male/14 female
Myasthenia gravis	18 positive (53%)
Other autoimmune conditions	3 (9%)
Other growths	7 (21%)
Death	2 non-thymoma related

Sample Characteristics

Table 2. Depicts the frequency of the WHO histological types.

| Type	Frequency
A	3
AB	6
B1	5
B2	7
B3	7
C	4

WHO Histological Types

The Patient Archiving and Communications System (PACS) used by all National Health Service (NHS) Scotland facilities was the program utilised for assessing the CT scans and radiological reports. The ITMIG database was used in conjunction with the Cardiac, Cardiology and Thoracic Health Information System (CATHI) at the Golden Jubilee National Hospital to retrieve the histopathological result. Statistical Package for the Social Sciences (SPSS) version 8 for Windows was used to analyse the data generated.

3. Methods

CT scans and radiological reports of these patients were compared with the definitive histopathological result. This was to assess if the pre-surgery CT scan gives enough information to accurately predict the post-surgical histological staging of these tumours. The ITMIG's comprehensive database was interrogated to ascertain the final histopathological Masaoka-Koga staging of each thymoma. This was double checked against the original report on the CATHI system. With training in use of PACS, an equivalent Masaoka-Koga stage for every thymoma pre-surgery was recorded. Figure 1 shows each thymic epithelial tumour stage as recorded on CT scans. The thymic epithelial tumour was recorded as stage I if the scan showed a completely encapsulated tumour; stage II if there was visible infiltration into the surrounding fatty tissue; stage III if there was invasion into neighbouring mediastinal organs or abutment of the great vessels; and stage IV if evidence of pleural or pericardial dissemination was present. This was double checked against the original report. The Masaoka-Koga system used in the methods, with associated survival rates, is displayed in Table 3. For statistical analysis, SPSS was used to cross-tabulate the two groups of results and perform a kappa coefficient to assess the level of agreement between the radiological and pathological staging.

(A) Stage I

(B) Stage II

(C) Stage III
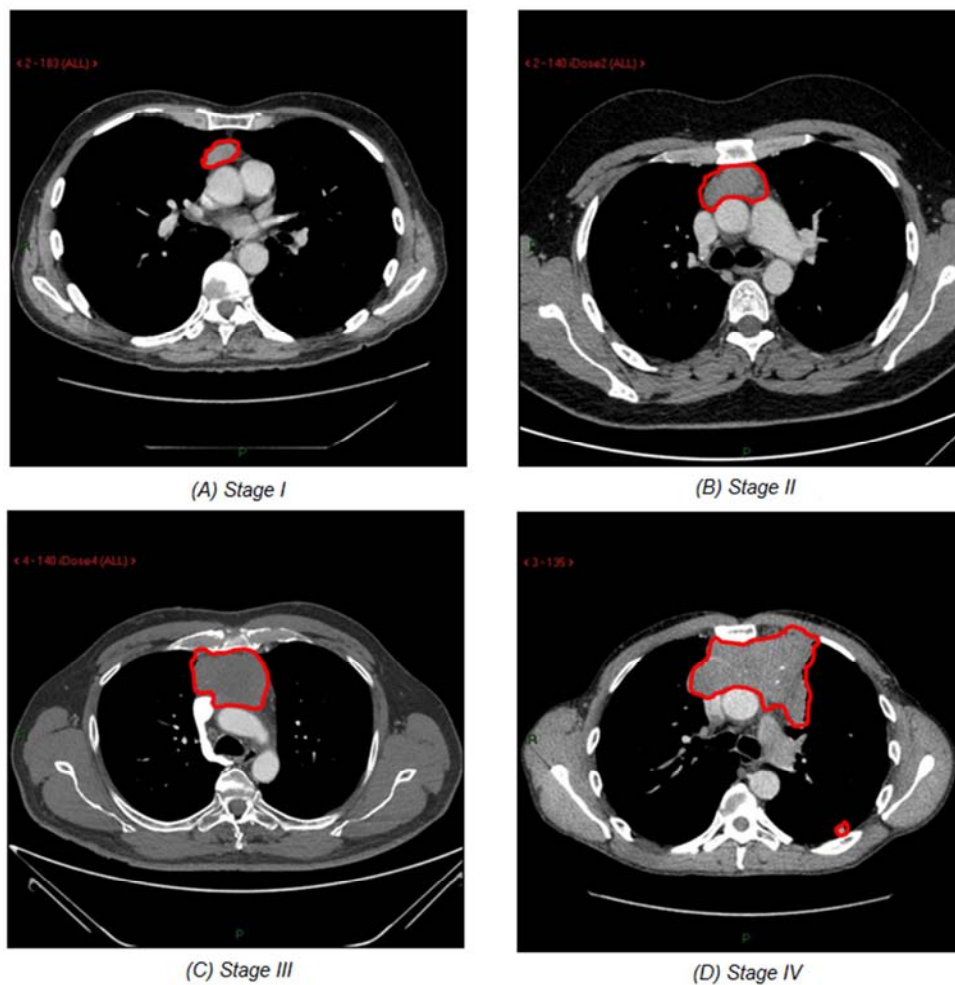
(D) Stage IV

Computed Tomography Images of Thymic Epithelial Tumour Stages

Figure 1. Shows CT scans of each thymic epithelial tumour stage with tumour tissue outlined in red: (A) Stage I; (B) Stage II; (C) Stage III; (D) Stage IV.

Table 3. *Displays the thymic epithelial tumour staging system adapted from the Masaoka-Koga system [11] with survival statistics [7].*

Stage	Description	10-year survival	15-year survival
I	Grossly and microscopically completely encapsulated tumour	80%	78%
II	A – Microscopic transcapsular invasion B – Macroscopic invasion into thymic or surrounding fatty tissue	78%	73%
III	Macroscopic invasion of neighbouring organs (pericardium, great vessels or lungs)	47%	30%
IV	A – Pleural or pericardial dissemination B – Lymphatic or haematogenous metastasis	30%	8%

Masaoka-Koga Staging System

4. Results

Figure 2 displays the frequency of each stage found by radiology and pathology. For radiology, 17 tumours were recorded as stage I; 11 recorded as stage II; 3 recorded as III; and 3 recorded as stage IV. For pathology, 14 tumours were found to be stage I; 12 were stage II; 5 were stage III; and 3 were stage IV. The number of CT stages agreeing with the pathology stages was 21 out of 34 (61.8%). For the 14 thymomas that were found to be stage I at pathology, the radiology agreed with 11 of them (78.6%). 5 out of 12 (41.7%) agreed for the stage II; 2 out of 5 (40%) for stage III and all 3 (100%) stage IV thymomas showed agreement between pathology and radiology. The important differentiation, with regards to treatment plans, is between stage II and III. The number of thymomas recognised as stage II at radiology but found to be stage III at pathology was 3. On the other hand, there was one thymoma that was overestimated as a stage III at radiology when it was in fact only a stage II. Table 4 represents a cross-tabulation of radiology and pathology stages. A full list of each result can be found in the Appendix.

Table 4. *Represents a cross-tabulation of radiology and pathology stages.*

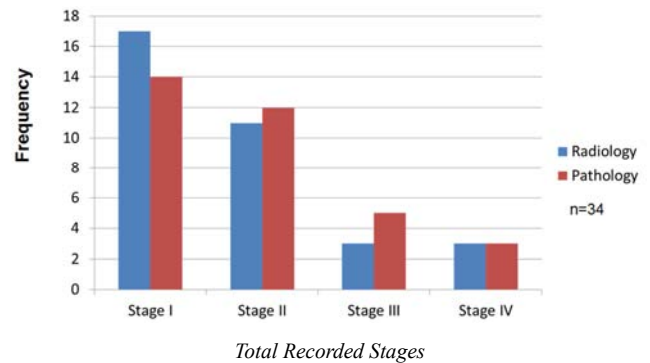|		Pathology				Total
		I	II	III	IV	
Radiology	I	11	6	0	0	17
	II	3	5	3	0	11
	III	0	1	2	0	3
	IV	0	0	0	3	3
Total		14	12	5	3	34

Radiology and Pathology Stages

The kappa coefficient performed came out as 0.42 ($p < 0.01$) which is in the range described as moderate agreement [12]. Therefore, the moderate agreement found between the radiology and pathology is statistically significant.

The histological types using the WHO classification system were recorded however one TET's grade was not available and another was an involuted thymic cyst which does not fit into this classification. For each thymic epithelial tumour, the highest grade found histologically was recorded; if a type B2 was found to have isolated foci of B3 cells then B3 was recorded.

Table 5 compares WHO histological types with Masaoka-Koga staging and shows that all type A and AB in this sample were either stage I or II. All stage III or IV thymic

epithelial tumours were type B1, B2, B3 or C.

Figure 2. *Displays the frequency of each recorded stage by radiology and pathology.*

Table 5. *Compares WHO histological types with Masaoka-Koga staging.*

WHO Type	Masaoka-Koga Staging			
	I	II	III	IV
A	1	2	-	-
AB	3	3	-	-
B1	2	2	1	-
B2	3	3	-	1
B3	3	1	2	1
C	-	1	2	1

WHO Histological Types and Masaoka-Koga Stages

5. Discussion

The moderate agreement shown in the results of this investigation between pre-operative radiological staging and post-operative histopathological staging suggests the methods used to assess thymic epithelial tumours via CT scan are quite effective but there is room for improvement. This finding is important as a founder of the International Thymic Malignancy Interest Group asked for the answer to this question shortly after this project was undertaken at their annual meeting: does the clinical stage of a thymic epithelial tumour match with the final outcome found once it is resected? Knowing the answer would allow oncologists to act with confidence when prescribing adjuvant therapy in the more advanced stages of thymic tumours [8]. The ITMIG has recommended the most commonly used Masaoka-Koga staging system due to its correlation with survival rates [13], [14]. However, as this focusses on pathological staging at the time of surgery, a method to clinically assess tumours allows the first treatment step to be decided.

As thymic epithelial tumours account for less than 1% of

adult malignancies [1], there is a limited amount of randomised evidence to analyse. This not only reduces the sample size available to each department and study undertaken but also makes any data collected at risk of being over-interpreted. As 61.8% of the CT scan assessments agreed with the final pathological report in this study, it is hard to initially comment on their success. As stage IV tumours have very discrete criteria, variation between radiology and pathology was not expected; this was the case. It could also translate to every hospital setting as metastasis would either be picked up upon suspected cancer patients' full-body CT scans and this status would not change upon pathological review (unless successful eradication occurs) or be missed completely.

Stage III tumours had the least successful CT scan agreement rate with 40% closely followed by stage II with 41.7%. It is interesting the point at which decisions for neo-adjuvant (before surgery) therapy are in contention – between stage II and III – is the one showing highest levels of disagreement. It seems the ability to differentiate capsular invasion and invasion into neighbouring organs radiologically requires strengthening. Perhaps the Masaoka-Koga staging system, which was adapted from the original Masaoka system, requires further modification to remove ambiguity. It does not define transcapsular invasion specifically or clarify how stage II and III relate to pericardium precisely. Other authors have criticised the marginal differences in survival rates between stage I and II and the wide range of invasion levels stage III can encompass [11]. On the other hand, it is important that studies conduct their reviews of cases using a standard protocol to reduce variation so a new system may not be what is required. Appreciation of the need to define subtle distinctions while maintaining the existing structure will allow consistent recording of thymic epithelial tumour cases.

Another aspect to consider is in differentiating between benign and malignant thymic tumours. Traditionally, benign growths have been assigned the name thymoma while the malignant varieties are called thymic carcinomas. There is wide variation in thymic tumours as some benign neoplasms may remain slow growing but others that were once thought benign show local invasiveness and pleural dissemination later in their clinical course. As this project encompasses all epithelial neoplasms of the thymus gland, the more inclusive term "thymic epithelial tumour" was used. It is the cell types and degree of undifferentiated proliferation that discern the grade classification of tumours. Furthermore, the adoption of the Masaoka system after 1981 has led to prognosis being based upon level of invasiveness rather than the cellular characteristics. One drawback of this is that we are unsure if the survival rates recorded and therefore the staging system applies to thymic carcinoma as well. As only 4 of the recorded cases in this study were found to be thymic squamous cell carcinomas, when graded at histopathology, they were still included to bolster the small sample size. As information about cellular types is only known if a cell biopsy is performed on the tumour, including the variable of

potentially more malignant growths could be needed to assess the diagnostic accuracy of CT scans.

Statistical analyses can be used to find accurate results. The use of Cohen's kappa coefficient in this project was to assess the level of agreement between two groups while taking into account the possibility of agreement occurring by chance. The resulting coefficient is a number from 0 to 1 suggesting no agreement and perfect agreement respectively. Although it is difficult to relate the significance of this coefficient due to reporter variance, it has been suggested that values 0–0.20 show slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect agreement [12]. Therefore, the reading of 0.42 in this investigation suggests moderate agreement between stage recording in radiology and pathology.

A Bland-Altman plot was created from the results to display the instances that radiology and pathology did not show exact agreement. However, due to the ordinal rather than sequential nature of the data, the plot showed a lot of overlapping. As it was not a successful visual aid, it was omitted from the methods and results. The plot can be found in the Appendix.

It is difficult to relate this result to other published data as there is little comparative work in measuring invasiveness by CT scan. This is due, in part, to few concrete radiological signs of stage III invasion; apart from the effects seen on blood vessel lumina; causing a belief that CT had a restricted role in thymic epithelial tumour staging [15]. One investigation into CT imaging solely assessed the ability to detect a thymic epithelial tumour in patients with myasthenia gravis. The average positive predictive value for this was only 39%. However, not only did this exclude the large proportion of thymic epithelial tumour patients without myasthenia gravis but also suffered from high inter-observer variance [16]. Also, many of the studies that have looked at the prognostic value of CT scans have used the World Health Organisation's histological classification to relate tumour morphology; rather than the Masaoka-Koga staging system used in the clinical environment [17]. There is agreement with the current project that CT scans may be used effectively to discriminate low-stage and high-stage thymic epithelial tumours; namely stage I and stage IV [18].

One retrospective study of 129 patients made a comprehensive correlation between pre-operative CT findings and "Masaoka clinical stage" of resected thymomas and found similar results to the current project. Their weighted kappa coefficient came out as 0.819 indicating a strong agreement between radiological and pathological staging [19]. A more recent study reported a weighted kappa coefficient of 0.621 [20]. These reports and the current project's result could encourage future prospective studies to analyse the predictive power of CT scans with less study bias.

There is some discussion about the benefit of using other imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET). CT scan is the most commonly used imaging modality in the diagnosis

of mediastinal masses [21]. There have been few investigations into the use of MRI in the staging of patients with a thymic epithelial tumour but it can be used commonly in patients unable to receive the contrast injections used for CT scans. It was found that MRI was superior to CT scans in the visualisation of the surrounding capsule and haemorrhage within tumours [22]. PET scans are layered over CT scans and depict "hot" areas in the body as regions with high cellular activity i.e. areas of increased proliferation suggesting malignancy. It has been shown that PET scans can identify thymic epithelial tumours containing more aggressive cell types but does not discern between lower and higher stages [23], [24]. With the discovery of high levels of insulin-like growth factor 1 receptor expression in thymic epithelial tumours, a new avenue of molecular marking to image and treat may open [25].

6. Limitations

Despite being one of the largest thoracic units in the United Kingdom, the rarity of thymic epithelial tumours will lead to continued shortage in sample numbers thereby making generalisability of results difficult. Furthermore, a sample taken from only Scotland does not allow for a diverse ethnic variance that a more global study could embrace. A multicentre study should be the next goal, alongside a multinational database for interrogation.

A possible limitation of this investigation is the use of pathological reports as an effective control. There is the potential that loss of orientation could occur when the thymus tumour is removed at surgery and the sample is sent to the histopathology lab. Effective communication between surgeon and pathologist is also required to prevent pathologists missing the origin of certain tissues in the sample (for example: mediastinal pleura). This could lead to incorrect staging [13]. However, this potential drawback would be observed in any study using information from pathological reports. In clinical practice, these reports are used, along with other clinical and diagnostic evidence, as the basis to guide patient treatment. Therefore, as this is the best information available to healthcare professionals, pathological reports could be deemed as a good control.

Another limitation of this project is the large number of different initial observers in both CT scan and histopathology reporting. Combined with a lack of standardised reporting protocol and expertise in diagnosing thymic epithelial tumours by CT scan (due to its rarity), there is likely a high inter-observer variance. One study showed only a "fair" agreement (kappa = 0.28) between radiologists in even correctly identifying a thymic epithelial tumour via CT scans of 34 patients with myasthenia gravis [16]. Again, a retrospective study relies on data obtained in a real clinical setting and different radiologists being on site at different times is unavoidable. Perhaps a prospective project similar to the current investigation involving a few more experienced reporters would allow for inter-observer variance to be assessed and taken into account.

Finally, the inherent limitation when assigning a Masaoka-Koga stage to a thymic epithelial tumour observed via CT scan is the inability for CT scans to observe microscopic qualities. As such, the distinction between stage IIA and IIB cannot be made radiologically. This is likely the most common reason for some stage II thymic epithelial tumours to be mistakenly reported as stage I by radiology. A well-defined, rounded thymus growth may appear to be contained within its capsule on a CT scan but any microscopic transcapsular invasion will be missed. Although this prevents the detailed comparison of radiology and pathology in the stage II sub-stages, stage I and stage II thymic epithelial tumours undergo the same preoperative treatment plan: complete surgical resection [14], [26]. There is also little difference in the prognostic value of comparing stage I and stage II with regards to survival rates [7]. Therefore, it is hoped that the inability to discern stage IIA on CT scan would have little impact on patients. Nevertheless, devising new radiological methods or developing upon old may allow more precise staging in the future.

7. Future Studies

The goals of this investigation have been achieved; to answer the simple question of whether preoperative CT scan observations can accurately predict the post-operative Masaoka-Koga staging of thymic epithelial tumours. However, future studies could address the limitations of this investigation upon replication. There is also the possibility to widen the scope of the project beyond that which was possible in the current time frame. The ITMIG database, used to assign Masaoka-Koga stages to each patient in the current sample, is used worldwide by surgeons to record diagnostic information for each patient with a thymic epithelial tumour. This results in over 900 cases available to be analysed and could give a definitive answer to the aim of this project. The current investigation has led to full ITMIG database access for the team at the Golden Jubilee National Hospital. The author intends to continue this work on a broader scale. Tracking patients to correlate their pre- and post- operative staging with 5- and 10- year survival rates could also enhance a future study. It would contribute to the small quantity of research carried out on the topic and give weight to any new results obtained.

8. Conclusion

The results from this study indicate CT scans are moderately successful in preoperative staging of thymic epithelial tumours. This may provide reassurance to clinicians relying on radiological information to make surgical and therapeutic decisions. Confidence in using CT scans in discerning the highest and lowest stages can be maintained. However, a uniform reporting technique backed with mortality evidence is required. With a framework to guide radiological reporting to correlate with Masaoka-Koga histopathological staging, standardisation could be achieved.

This would increase reliability of the assessment of this rare tumour. The use of other imaging techniques, such as MRI, may provide useful added information to enhance observations. The future lies in adapting current practice to enhance the accuracy of pre-operative staging.

Abbreviations

CATHI – Cardiac, Cardiology and Thoracic Health Information System
CT – Computed Tomography
ITMIG – International Thymic Malignancy Interest Group
MRI – Magnetic Resonance Imaging
NHS – National Health Service
PET – Positron Emission Tomography
PACS – Patient Archiving and Communications System
SPSS – Statistical Package for the Social Sciences
TET – Thymic Epithelial Tumour
WHO – World Health Organisation

Appendix

Table A1. *Table of Data.*

Patient Number	Radiology Stage	Pathology Stage	WHO Classification
1	II	I	Involuted thymic cyst
2	III	III	B3
3	I	I	AB
4	II	IIB	B2
5	II	III	B3
6	IVA	IVA	C
7	I	IIA	AB
8	I	I	B3
9	II	I	B3
10	II	IIA	B1
11	III	IIA	A
12	I	IIA	AB
13	I	I	B1
14	I	I	B2
15	I	I	AB
16	IVA	IVA	B2
17	I	I	A
18	I	I	B1
19	I	IIA	B1
20	I	IIA	B2
21	I	I	B2
22	II	IIA	A
23	IVA	IVA	B3
24	III	III	C
25	II	IIA	B3
26	I	IIB	B2
27	II	III	C
28	II	IIB	C
29	I	I	AB
30	II	III	B1
31	II	I	B3
32	I	I	Report unavailable
33	I	I	B2
34	I	IIB	AB

Appendix Table lists each radiology and pathology result.
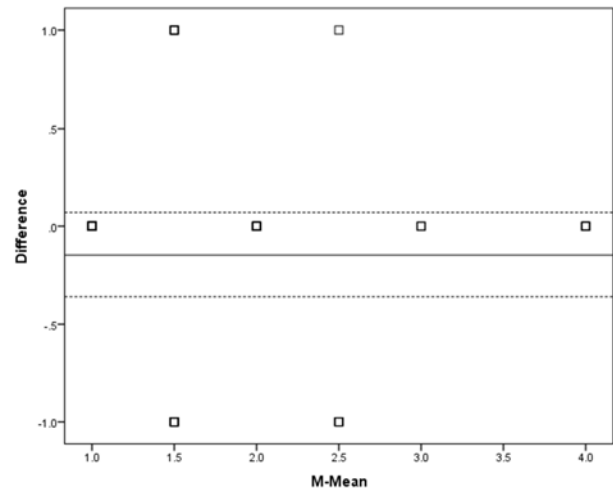
Bland-Altman Plot

Figure A1. *Bland-Altman plot comparing radiology and pathology.*

Appendix figure shows a Bland-Altman plot comparing radiology and pathology where 0 shows agreement and -1 and 1 show disagreement. The frequency of each instance of agreement is emphasised by the squares becoming darker. The solid line represents the mean while the dotted line is the standard deviation.

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