Original Article

# Outcome of Nephrectomies in Malta since 2000

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**Abstract**

Aim: To audit the oncological results and perioperative surgical outcome of nephrectomies performed in Malta since year 2000.

Method: A retrospective index case list of all nephrectomies carried out by three urological surgeons at St Luke's and Mater Dei Hospitals from 1st September 2000 to 31st March 2012 was compiled from departmental data. Clinical, radiological and histological data were compiled from the case notes and hospital intranet computerised investigation results. Clinical staging of all patients was revised using the *Union Internationale Contre le Cancer* TNM staging 2009. All the patients who underwent nephrectomy for clear cell renal cell carcinoma were stratified according to individual predicted prognosis based on the SSIGN score developed by the Mayo clinic.

Results: Between September 2000 and March 2012, 319 nephrectomies were carried out at the Urology Unit, of these 288 were carried out for malignancy, 218 of which were clear cell renal cell carcinoma (RCC). 112 complications were recorded for the whole cohort; two patients died from perioperative complications. 80 patients passed away, 51 of these as a direct consequence of their renal cell cancer. Median duration of follow up was 42.7 months. A Cox model reveals that a SSIGN score greater than 6 significantly worsens survival rate for RCC ($p<<0.001$).

Conclusion: Morbidity following surgery, mortality rates, and oncological results in our single centre study are acceptable when compared to larger series.

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## Introduction

Despite the progress made in recent decades with the elucidation of various molecular pathways involved in the carcinogenesis of renal cell carcinoma of the kidney[1-4] which has paved the way for the development and introduction of systemic targeted therapies, the treatment of renal cell cancer remains predominantly surgical, with a paucity of alternative or adjunctive oncological options available to patients suffering from this aggressive disease.

The indication for surgical treatment has also widened with the consolidation of cytoreductive nephrectomy in metastatic disease[5-6] and establishment of laparoscopic techniques outside of centres of excellence.[7-8]

Nephrectomy is also sometimes indicated in severe benign diseases of the kidney making it a commonly performed operation in most urological units worldwide.

Cancer of the kidney and ureter was seventh most commonly diagnosed cancer in Maltese males in 2012 with an age standardised incidence of 15.0/100,000 [9] and represents a significant proportion of the patients seen at our institution's Urology Unit.

The increasing use of cross sectional imaging for investigation of various medical complaints has also resulted in an increasing incidence of incidental asymptomatic renal tumours, a phenomenon common to most urology units in the developed world. [10]

## Method

A retrospective index case list of all nephrectomies carried out by three urological surgeons at St Luke's and Mater Dei Hospitals from 1st September 2000 to 31st March 2012 was compiled from departmental data. Operative data relating to procedures carried out within our Urology Unit is compiled in a prospective manner using a Microsoft Access®-based database, allowing accurate and reliable retrieval of the index case list.

Clinical presentation, prognostic factors, histology, radiological characteristics, surgical technique, post-operative morbidity and mortality, length of hospital stay and vital status were compiled from the case notes and hospital intranet radiological and clinical databases.

Survival data was corroborated with death certificates obtained from the Department of Health Information.

Staging of all patients was revised using the TNM staging *Union Internationale Contre le Cancer* TNM staging 2009, which has been externally validated in 2011.[11,12] Information from preoperative CT scans and histopathological report of the resected specimen were combined to restage all the patients in the cohort.

All the patients who underwent nephrectomy for clear cell renal cell carcinoma were stratified according to individual prognosis based on the Stage, Size, Grade, Necrosis Score Algorithm (SSIGN) developed by the Mayo clinic [13] and recently externally validated in a European study. [15] As the SSIGN score is validated for use only in clear cell renal cell carcinoma, patients whose pathology was not clear cell renal cell carcinoma were excluded from survival analysis, although these records were included in other analyses. 35 patients who developed a second malignancy (excluding squamous cell carcinoma or basal cell carcinoma of the skin) during the study period were excluded from this analysis.

**Results**

Patient and tumour characteristics are shown in Table 1. 319 patients underwent nephrectomy between September 2000 and March 2012. 288 patients underwent nephrectomy for tumour, of these tumours 218 were clear cell renal cell carcinomas. Other indications for nephrectomy included inflammatory or infective pathologies (26), benign masses (36), polycystic kidney disease (4) and vesico-ureteral reflux with dysplastic kidney (1). 75% (*n*=241) of the patient cohort were diabetic, other risk factors for renal malignancy included current smoking at time of surgery (16.9%, *n*=54), smoking history (14.4%, *n*=46) and positive family history (1.5%, *n*=5).

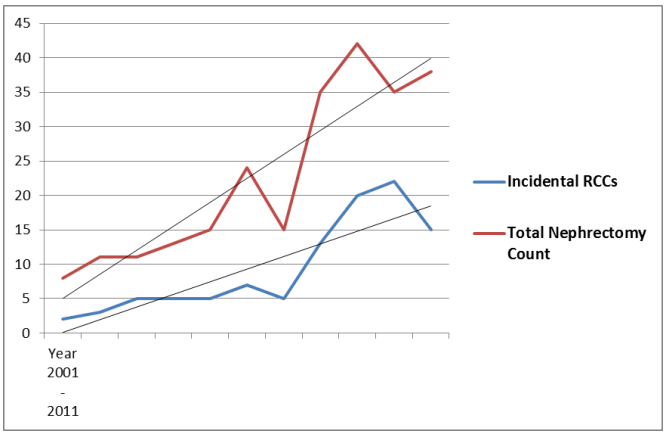
The local incidence of incidentally detected kidney tumours has been rising over the last decade (35%, *n*=115) (Figure 1). The total number of nephrectomies performed per year has also been increasing in parallel over the study period. Loin pain was the presenting symptom in 24% (*n*=82), gross haematuria in 23% (*n*=79), pyrexia of unknown origin in 3% (*n*=11), anaemia in 2% (*n*=8) and abdominal mass in another 2% (*n*=6). 11 patients (3%) presented with uncommon symptoms, such as nasal congestion from posterior nasal space metastasis, visual deterioration from occipital lobe metastasis and skull metastasis. Information on clinical presentation is not available in 26 patients (8%).

The majority of the patients underwent open radical nephrectomy (70%), followed by open partial nephrectomy (Table 1). One patient underwent joint procedure with cardiothoracic surgeons with radical nephrectomy, inferior vena cava exploration and removal of right atrial tumour thrombus under cardio-pulmonary bypass.

***Table 1**: Patient and Tumour Characteristics*

| **Total number of patients** | **319** |
|---|---|
| **Nephrectomy for tumour** | **288** |
| Males (%) | 191 (60) |
| Females (%) | 128 (40) |
| Age (years) mean (range) ± SD | 58.7 (22 - 90) 11.85 |
| Radiological Size (cm) mean (range) | 6.3 (1 -20) |
| Tumour location | |
| Upper pole | 92 |
| Central | 90 |
| Lower pole | 77 |
| Complete renal infiltration | 10 |
| Renal pelvis | 11 |
| Ureter | 4 |
| Not available | 4 |
| TNM Distribution | |
| Localised at presentation | |
| T1a N0 M0 | 71 |
| T1b N0 M0 | 51 |
| T2a N0 M0 | 15 |
| T2b N0 M0 | 19 |
| T3a N0 M0 | 29 |
| T3b N0 M0 | 7 |
| T3c N0 M0 | 2 |
| T4 N0 M0 | 0 |
| Metastatic at presentation | |
| T2a N1 M0 | 1 |
| T3a N1 M0 | 1 |
| T3b N1 M0 | 1 |
| T4 N1 M0 | 1 |
| T1b N0 M1 | 1 |
| T2b N0 M1 | 4 |
| T3a N0 M1 | 4 |
| T3b N0 M1 | 1 |
| T3a N1 M1 | 1 |
| T3b N1 M1 | 1 |
| T3c N1 M1 | 2 |
| T4 N1 M1 | 1 |
| Surgical Procedure | |
| Open Radical Nephrectomy | 225 |
| Open Partial Nephrectomy | 34 |
| Nephroureterectomy | 15 |
| Simple Nephrectomy | 15 |
| Laparoscopic Partial | 13 |
| No Data | 11 |
| Laparoscopic Radical | 5 |
| Open Radical and Sternotomy | 1 |
| Fuhrman grade (mean) | 2.33 |

***Figure 1**: Incidence of incidental tumours and total nephrectomy surgeries over study period*




Morbidity and mortality data are shown in Table 2. A total of 62 patients (20%) suffered from a post-operative complication. 46 patients suffered one complication, 12 patients suffered two events and four patients suffered three complications.

After excluding post-operative transfusion (9.7%), important complications included pneumonia (15 patients), deterioration in renal function requiring temporary dialysis (8 patients), wound complications (16 patients) and intestinal obstruction requiring laparotomy (3 patients). Two patients were rendered anephric by surgery in the context of adult polycystic kidney disease, and the need for permanent dialysis was determined by pre-existing end-stage renal failure.

Two patients died within 30 days of surgery from complications related to the nephrectomy, one patient sustained a myocardial infarct followed by cardiac arrest and a second patient developed DIC after severe haemorrhage and multiple blood transfusions.

Oncological results are shown in Table 3. 288 patients who had histologically proven renal cancer were included for analysis of oncological outcome. Patients whose final histological diagnosis was clear cell renal cancer ($n$=218) were stratified and analysed according to the SSIGN score. This scoring system is based on the pathological tumour stage, tumour size, tumour necrosis, nodal status and presence of distant metastasis. Every patient with known clear cell renal cell carcinoma was included in one of five risk groups. Crude survival and cancer specific survival for each group was calculated and showed using the Kaplan Meier method. (Figures 2 and 3).

The same cohort of patients was then divided into two risk groups using a cut off of SSIGN score 6, with the group having a score of > 6 having a statistically significant survival disadvantage ($p$<0.001). (Figures 4 and 5).

***Table 2**: Summary of Complications*

| | | | |
|---|---|---|---|
| Haematological | | Renal/urological | |
| Transfusion | 28 | Temporary Dialysis | 8 |
| DVT | 2 | Perinephric/retroperitoneal haematoma | 3 |
| Febrile reaction to transfusion | 1 | Permanent dialysis (anephric) | 2 |
| DIC | 1 | Renal dysfunction - no dialysis | 1 |
| | | UTI | 1 |
| Respiratory | | Clot colic with obstruction | 1 |
| Pneumonia | 15 | Calculous obstruction single kidney | 1 |
| Intraoperative desaturation | 1 | Urocutaneous fistula | 1 |
| Pleural effusion | 1 | | |
| Cardiovascular | | Drug related | |
| MI/cardiac arrest | 1 | Opiate overdose | 3 |
| Arrhythmia (cardioversion) | 1 | Drug rash | 1 |
| Arrhythmia (pharmacological rx) | 2 | Hand and Foot Syndrome (TKIs) | 1 |
| Angina | 2 | | |
| Cerebrovascular event | 1 | | |
| GIT/Intrabdominal | | Body Wall | |
| Bowel obstruction (conservative) | 3 | Wound infection | 7 |
| Bowel obstruction (laparotomy) | 3 | Incisional hernia | 7 |
| GI bleed | 2 | Wound haematoma | 2 |
| Psoas abscess (surgical drainage) | 1 | | |
| Systemic | | Perioperative death | |
| Sepsis | 3 | DIC | 1 |
| Hyperglycaemia | 2 | MI | 1 |
| Acute confusion | 1 | | |

***Table 3**: Follow up data*

| | |
|---|---|
| Follow up (days) mean (range) | 1282 (13 - 4246) |
| Adjuvant Oncological Treatment | |
| Systemic chemotherapy | 8 |
| External beam radiotherapy | 15 |
| Interferon | 2 |
| Tyrosine kinase inhibitor | 7 |
| Local Recurrence n (%) | 10 (3.4) |
| Distant Metastasis n (%) | 43 (14.9) |
| Metastasis free survival (metastatic pts only) (days) mean (range) | 566 (8 - 3186) |
| Local recurrence free survival (recurring pts only) (days) mean (range) | 280 (103 - 645) |
| Metastasis sites n of pts, (%) | |
| Lung | 21 (30) |
| Bone | 12 (17) |
| Liver | 9 (13) |
| Retroperitoneal LNs | 7 (10) |
| Adrenal | 6 (8) |
| Brain | 3 (4) |
| Pancreas | 2 (3) |
| Other | 11 (15) |
| Second Primary Tumours n of pts, (%) | 35, (12%) |
| Site of second primaries, n of pts | |
| Bladder | 8 |
| Prostate | 6 |
| Colon | 6 |
| Breast | 5 |
| | |
| Lung | 3 |
| | |
| Other | 7 |

***Figure 2**: 10 year crude survival stratified per SSIGN groups A—E*

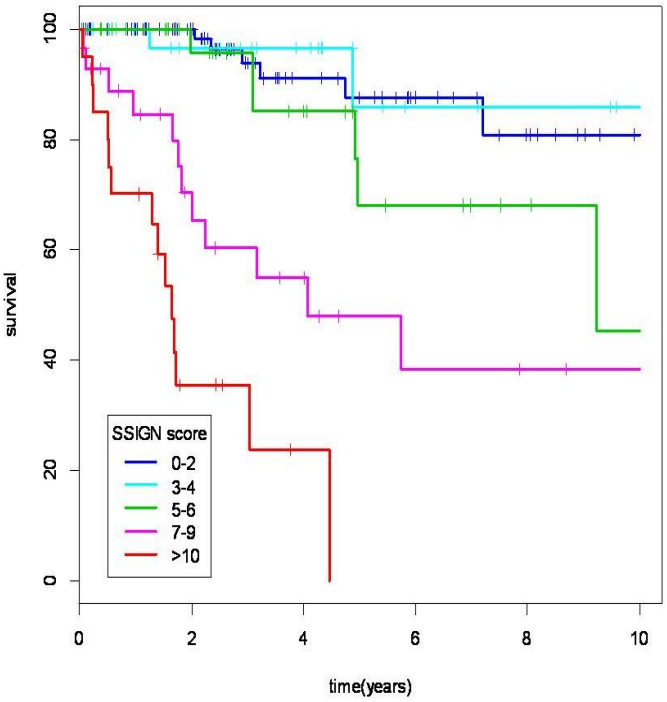



***Figure 3**: 10 year cancer specific survival stratified per SSIGN groups*

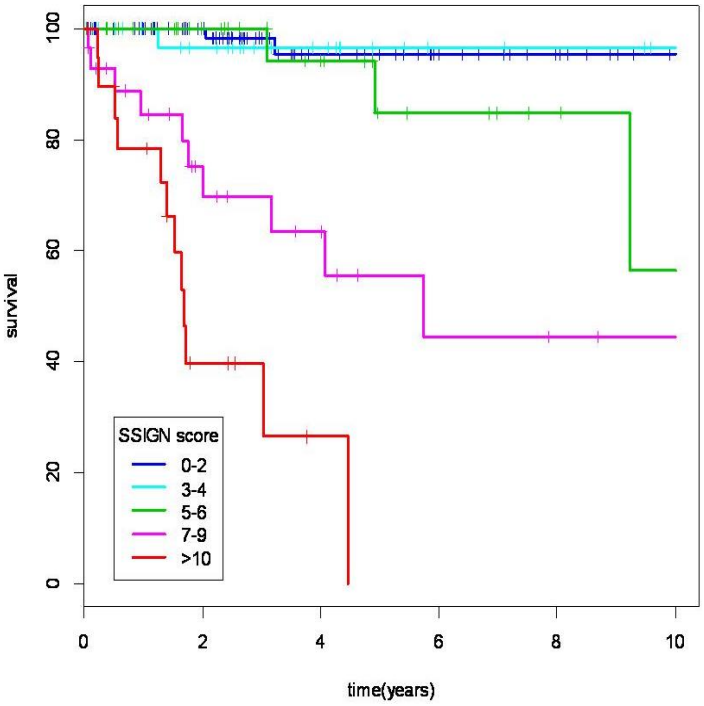


***Figure 4**: 10 year crude survival stratified per low/ high risk groups*

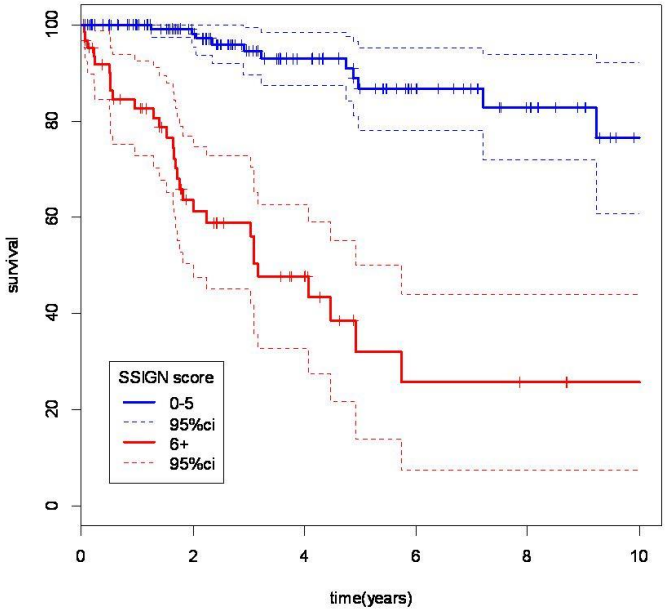
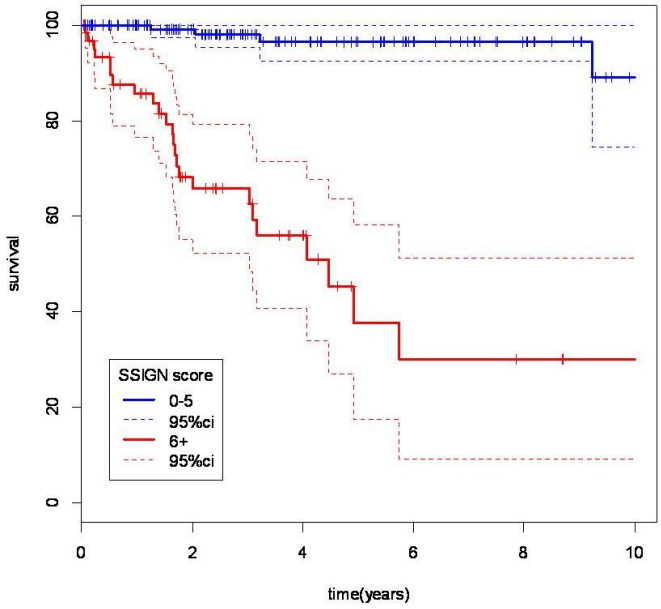



***Figure 5**: 10 year cancer specific survival stratified per low/ high risk groups*




## Discussion

In this series, nephrectomy resulted in acceptable morbidity rates. The post-operative 30 day surgical mortality rate of 0.62 % compares well with published figures ranging from 0.77 to 2.3%. [16] Post-operative complication rates are also in line with other published series with a total morbidity rate of 20% (with studies quoting complication rates between 2 and 35%). [17, 18]

Oncological results in the clear cell carcinoma group also compare favourably with larger series published by tertiary high volume centres (Table 4). Our results in the very poor prognosis group are significantly worse, however these patients were mostly (19 out of 20) patients who presented with metastatic disease and had cytoreductive or palliative nephrectomy to alleviate symptoms. These metastatic patients were not included in the series by Frank *et al* [13] or Zigeuner *et al* [14] and this may explain the differences in outcomes observed. In our series the SSIGN score was confirmed to be a good indicator of predicted survival in clear cell carcinoma patients undergoing radical or partial nephrectomy.

***Table 4**: 10 year Cancer Specific Survival stratified by SSIGN score groups*

| SSIGN Score (0 - 16) | Number of pts per group (Local Series) | Local Series (*n* = 201) | (Mayo Clinic) Frank I *et al* – 10 yr survival (*n* = 1801) | Zigeuner *et al* - 10 yr survival (*n* = 2333) |
|---|---|---|---|---|
| 0 - 2 | 85 | 95% | 97% | 93% |
| 3 - 4 | 33 | 96% | 78% | 72% |
| 5 - 6 | 35 | 56% | 57% | 46% |
| 7 - 9 | 28 | 23% | 30% | 22% |
| ≥10 | 20 | 0% | 19% | 5% |

This series also outlines local trends in kidney cancer surgery, with partial nephrectomy slowly taking over radical nephrectomy as the technique of choice, [19, 20] in accordance with European Association of Urology guidelines.[21] Partial nephrectomy, although being a complex and challenging procedure, affords preservation of renal function which translates lower long term cardiovascular mortality and better overall survival, compared to radical nephrectomy.[22-24] The introduction of laparoscopic techniques into local practice over the last few years is also translating in lower patient morbidity.

Our study has some limitations and numerous strong points. Being the only urology unit in the country, follow up is mostly complete with no patients lost to follow up because of migration. Duration of follow ups is adequate with 10 year survival being presented rather than the traditional 5 year survival rates. Patients readmitted with post-operative complications are cared for by the same unit, so recording morbidity is an easier task. Mortality data was corroborated by death certification data obtained from the National Cancer Registry to minimise inaccuracy.

Limitations include those inherent to a retrospective audit, including incomplete data, reliance on potentially inaccurate medical notes and bias. Recorded complications were not graded according to a validated severity score because of scant clinical details which precluded accurate stratification. The performance status, co-morbidity and ASA score were not recorded, factors which would be expected to influence post-operative complications rates.

Data regarding BMI and blood pressure were not recorded, both obesity and hypertension now being considered as risk factors for kidney cancer carcinogenesis. The issue of obesity and metabolic syndrome could have significant local importance, as shown by the high incidence of diabetics in our cohort.

Lastly, cancer specific survival rather than overall survival was considered as the hard oncological end point, whilst overall survival might represent oncological outcomes in a more clinically meaningful way.

## Conclusion

Surgical morbidity and mortality rates and oncological results in our single centre study compare well to larger series. Over the study period changes in international guidelines and progress in surgical techniques have been adapted to our local practice with good effect.

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