

Paper I

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Renal Cell Carcinoma: Gender Difference in Incidental Detection and Cancer-specific Survival

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Objective: To look for an increase in the incidental detection of renal cell carcinoma (RCC) over the last two decades and to see if different patterns of healthcare use for men and women have implications for tumour detection and survival.

Material and Methods: We present an historical series of 368 consecutive patients treated with nephrectomy for RCC during the period 1978–2000. The patients were classified according to detection mode (incidental or symptomatic disease), TNM stage and cancer-related death.

Results: The frequency of incidentally detected RCC (IRCC) increased from 21.1% to 34.7% between the first and second decades of the study. The IRCC group had significantly more low-stage (I–II) tumours ($p = 0.002$), a smaller tumour size ($p < 0.0001$) at operation and significantly better cancer-specific survival ($p = 0.0048$) than the symptomatic renal cell carcinoma (SRCC) group. The frequency of women was significantly higher in the IRCC group than in the SRCC group ($p = 0.02$). Females had significantly more low-stage (I–II) tumours ($p = 0.02$) and better cancer-specific survival ($p = 0.05$) than males.

Conclusions: The number of incidentally discovered renal tumours is increasing. IRCC have lower TNM-stage and are smaller than SRCC. IRCC have better long term cancer specific survival than SRCC. The better survival rate found in females may be due to more extensive use of the healthcare system by females than males.

Key words: disease-free survival, health services, neoplasm staging, nephrectomy, renal cell carcinoma, women's health.

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Renal cell carcinoma (RCC) is responsible for 2.2% of new cancers discovered annually in Norway (1). The diagnosis of RCC is made either as a result of investigation of patient symptoms or as an incidental finding. The classic combination of symptoms suggesting RCC is macroscopic haematuria, flank pain and a palpable tumour. The presence of these symptoms, however, often seems to reflect either local tumour invasion or even metastatic disease. Incidental renal cell carcinomas (IRCCs) have been reported to be smaller and of lower stage ("stage migration") (2, 3) than symptomatic renal cell carcinomas (SRCCs). However, other reports have concluded that no such difference exists (4, 5). Recent reports have shown an increase in IRCCs over the last decade, probably due to more widespread use of new imaging techniques, such as ultrasound and computerized tomography (CT) (6, 7).

In an attempt to demonstrate a possible shift from symptomatic to incidentally discovered tumours in Norway, we reviewed our 20-year experience with RCCs. The male:female ratio of RCCs in Norway is reported to be 1.7:1 (1), comparable to reports from

other countries (3). Most of those reports showed the same male:female distribution in both SRCC and IRCC groups. Tsui et al. (2), however, demonstrated a higher proportion of females in the IRCC group. The fact that women in Norway visit their physician more often than men (8, 9) challenged us to look for possible differences in tumour stage and survival rates as a function of gender.

MATERIAL AND METHODS

The material consisted of 368 consecutive patients treated with nephrectomy for RCC at Oppland Central Hospital – Lillehammer ($n = 177$) between 1978 and 2000 and at Aker University Hospital ($n = 191$) during the 20-year period 1978–97. The study was retrospective. All patient records were reviewed. Information about the causes of death was collected from these records or from the national death certificates held by Statistics Norway.

Renal cancer-related symptoms included palpable tumour, haematuria (both macroscopic and micro-

Table I. Frequency (%; with numbers of patients in parentheses) of IRCC according to stage during the two time periods

Stage	1978–87	1988–2000	<i>p</i>
I	43.8 (14/32)	40.8 (31/76)	Not significant
II	21.1 (4/19)	34.6 (9/26)	0.13
III	15.7 (11/70)	34.6 (28/81)	<0.05
IV	9.9 (3/31)	21.2 (7/33)	<0.05
All stages	21.1 (32/152)	34.7 (75/216)	<0.001

scopic), flank pain and signs of cachexia related to the disease. Incidentally diagnosed cancers were considered to be tumours discovered during investigations performed for reasons other than for the renal cancer-related symptoms mentioned above. Tumours discovered during investigation due to highly elevated erythrocyte sedimentation rate (ESR), without any other symptoms, were also classified as incidental.

The tumours were staged according to the TNM classification system (International Union Against Cancer 1997 revision) (10).

Statistical analysis

Kaplan–Meier survival estimates were used for survival analysis and the log rank test was used for comparison of survival between groups. For statistical analysis Student's *t*-test and the χ^2 test were used. For multivariate analysis, Cox's proportional hazard model was used. A *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

IRCCs were present in 107/368 patients (29.1%) and 261/368 patients (70.9%) had SRCCs. However, during the last period (1988–2000) significantly more of the tumours were incidentally discovered than during the preceding decade (1978–87) ($p < 0.001$). The overall proportion of incidental RCCs increased from 21.1% in the first period to 34.7% in the latter.

An increase in IRCCs could be demonstrated for stage II–IV tumours, but surprisingly not for stage I tumours (Table I). Among patients with IRCCs, 42.1% had stage I tumours, 12.1% stage II, 36.4% stage III and 9.3% stage IV. Corresponding figures for SRCCs

Table II. Mean size of tumour (cm) in the IRCC and SRCC groups according to stage

Stage	IRCC	SRCC	<i>p</i>
I	4.42	4.73	Not significant
II	9.37	9.75	Not significant
III	7.32	7.83	Not significant
IV	7.5	8.97	Not significant
All stages	6.19	7.57	<0.0001

Table III. Distribution (%) of the surgical approach for nephrectomy within the IRCC and SRCC groups

Surgical approach	IRCC	SRCC
Extraperitoneal	18.7 (<i>n</i> = 20)	18.8 (<i>n</i> = 49)
Transabdominal	77.6 (<i>n</i> = 83)	72.4 (<i>n</i> = 189)
Thoracoabdominal	3.7 (<i>n</i> = 4)	8.8 (<i>n</i> = 23)

were 24.1%, 12.3%, 42.9% and 20.7%, respectively. There were significantly more low-stage (I–II) tumours in the IRCC group than in the SRCC group ($p = 0.02$). No differences with regard to detection and diagnosis between stage I–II and stage III–IV tumours in the IRCC group were identified in this retrospective material.

Mean tumour size was significantly smaller in the IRCC group (6.19 cm; median 6.0 cm) than in the SRCC group (7.53 cm; median 7.0 cm) ($p < 0.0001$). In terms of the individual tumour stages, mean tumour size was smaller in the IRCC group but none of the differences were statistically significant (Table II).

Extraperitoneal, transabdominal and thoracoabdominal approaches were the three types of surgical approach used for nephrectomy. Table III shows the distribution of these different surgical approaches in the IRCC and SRCC groups. No statistically significant difference in surgical approach could be demonstrated. Between the two time periods there was a significant increase in the use of the transabdominal approach ($p = 0.03$) (Table IV).

Cancer-specific survival curves are shown in Fig. 1. The 5-, 10-, 15- and 20-year cancer-specific survival rates were 61.9%, 52.0%, 44.1% and 40.9%, respectively in the SRCC group. For the IRCC group the corresponding figures were 81.2%, 76.1%, 60.5% and 60.5%. Survival was significantly better in the IRCC group ($p = 0.0048$). For the individual tumour stages, significant differences between IRCCs and SRCCs could not be demonstrated.

Patients operated on during the last time period (1988–2000) had significantly better 5- and 10-year cancer-specific survival rates than patients operated on during the preceding decade (71.5% and 62.6% vs 60.7% and 52.0%, respectively; $p = 0.035$)

Mean age at operation was 67 years (range 15–90 years) in the IRCC group and 63 (range 37–88 years)

Table IV. Distribution (%) of the surgical approach for nephrectomy within the two time periods

Surgical approach	1978–87	1988–2001
Extraperitoneal	24.3 (<i>n</i> = 37)	14.8 (<i>n</i> = 32)
Transabdominal	66.4 (<i>n</i> = 101)	79.2 (<i>n</i> = 171)
Thoracoabdominal	9.2 (<i>n</i> = 14)	6.0 (<i>n</i> = 13)

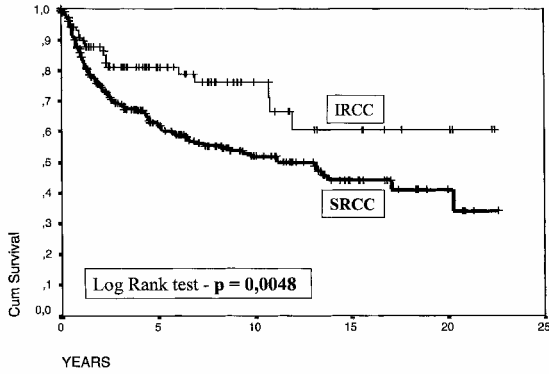


Fig. 1. Kaplan-Meier cancer-specific survival in patients with IRCC ($n = 107$) and SRCC ($n = 261$).

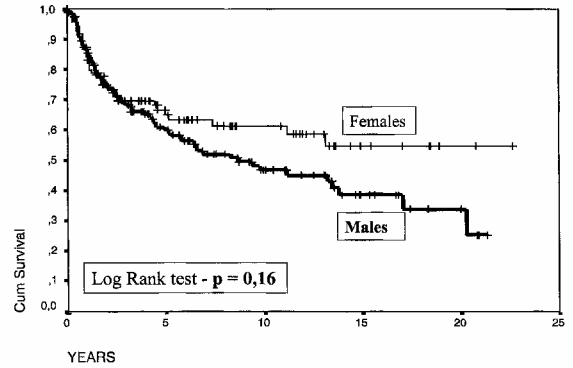


Fig. 3. Kaplan-Meier cancer-specific survival in females ($n = 96$) and males ($n = 165$) with SRCC.

years in the SRCC group. Men had a lower mean age at operation (63 years) than women (65 years).

The male:female ratios were 50.5:49.5 in the IRCC group and 63.2:36.8 in the SRCC group and this difference was statistically significant ($p = 0.02$). Similar sex distributions were found during the two time periods. There were significantly more low-stage (I-II) tumours at diagnosis in females than males ($p = 0.02$). Such a tendency could be demonstrated in both the SRCC and IRCC groups. No difference in tumour size between men and women could be demonstrated.

With regard to cancer-specific survival, higher long-term survival rates were demonstrated for women (Fig. 2). This difference was statistically significant ($p = 0.05$) and is explained by better female survival in the SRCC group (Figs 3 and 4) and the relatively higher proportion of women in the IRCC group.

There was higher perioperative mortality (<30 days) (3.4% vs 1.8%) and a greater proportion of reoperations (3.4% vs 1.8%) in the SRCC group. These differences were almost statistically significant ($p = 0.06$ in both cases). However, other postoperative complications were evenly distributed between the groups.

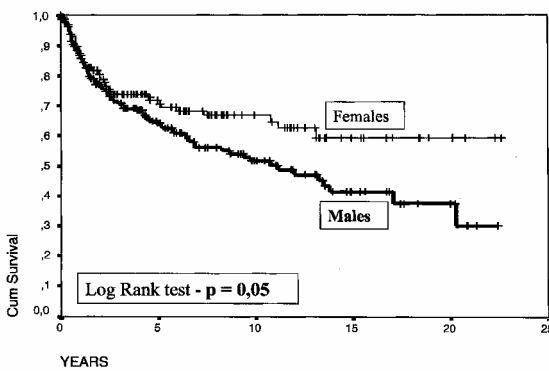


Fig. 2. Kaplan-Meier cancer-specific survival in females ($n = 149$) and males with RCC ($n = 219$).

Multivariate analysis was performed in order to identify independent prognostic variables. Tumour stage was the only significant independent prognostic factor. Age, size of tumour, sex, period of operation and incidental detection were not found to be independent prognostic factors.

Comparing the two time periods, our material showed a marked shift in the mode of tumour detection. Intravenous urography for detection and selective renal angiography for final diagnosis were the dominant imaging techniques used in the first period, with ultrasound and CT, respectively predominating in the latter. CT equipment was first installed at Aker University Hospital in 1982 and at Oppland Central Hospital in 1985. In combination with ultrasound, CT became the main diagnostic tool during the latter part of the first time period.

DISCUSSION

The major problem when discussing IRCC and SRCC is to define real and uniform criteria for classifying incidentally discovered kidney cancer. Varying defini-

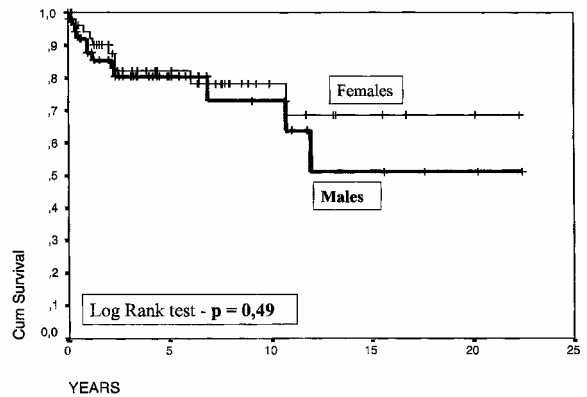


Fig. 4. Kaplan-Meier cancer-specific survival in females ($n = 53$) and males ($n = 54$) with IRCC.

tions from report to report make comparison between different materials difficult. Elevated ESR is an excellent example. Gudbjartsson et al. (11) defined it as an incidental finding, whilst Homma et al. (12) described it as a marker of symptomatic disease. There is a need for a common international consensus concerning which tumours should be categorized as incidental. Our definition of IRCC is shared by some authors but differs from that of others.

Skinner et al. (13), in 1971, reported that only 7% of RCCs were incidentally discovered. During the last two decades the incidence of IRCC has been reported to have increased (7, 12) due to the widespread use of new imaging techniques (6, 7). Hellsten et al. (14), in their 1958–69 autopsy series published in 1990, showed that only one-third of RCCs present at autopsy had been detected before death. New data from the Norwegian Cancer Registry (1) showed that only 2.7% of total RCCs were found incidentally at autopsy in 1997. The increase in IRCCs is probably due to new imaging techniques detecting tumours that previously would never have been detected. Support for this hypothesis is provided by the fact that IRCCs are found more in older age groups, as shown both in this study and by others (2, 3). These findings, however, cannot be regarded as logical. A better guess would be that IRCCs should be found in younger patients, because they are detected at earlier stages. In our opinion, this would have been correct if tumour detection was the result of population screening. In this Norwegian material, however, patients were referred for investigation as a result of some sort of health problem. Older people have more health problems and therefore in smaller studies like ours, this may result in a higher average age in the IRCC group.

The significant increase in IRCCs in our series compares well with other recent reports in the literature. In contradiction of our expectations we discovered increases in IRCCs between the two studied periods for the three highest tumour stages, but not for stage I. No convincing explanation can be given for this, but the percentage of stage I IRCCs in the 1978–87 material was remarkably high.

The surgical approach for nephrectomy was almost identical in the IRCC and SRCC groups. There was, however, a significant increase in the use of the transabdominal approach between the first and second periods. The mode of detection does not influence the choice of surgical approach. In the early 1980s reports showed better survival figures for RCCs when a transabdominal approach was used (15–17). The increase in the use of the transabdominal approach is a probable explanation for these results. The higher rate of thoracoabdominal operations in the SRCC group is not surprising, as this approach is used only in cases of very large tumours.

In this series, average tumour size was smaller and the proportion of low-stage tumours higher in the IRCC group. Both these results compare well with the figures reported by Tsui et al. (2).

A positive effect of IRCC on survival has been suggested in several reports (2, 7, 11). The study by Mevorach et al. (4), however, concluded that IRCC patients do not have better prognosis with regard to survival. Bos et al. (7) reported a better survival rate in the IRCC group, but were not able to demonstrate a lower T stage in the same group.

In our series there was significantly higher long-term survival in the IRCC group than in the SRCC group. Similar survival rates were found for all four tumour stages, indicating that “stage migration” towards lower stages is responsible for the overall significant difference in survival. The survival rates for both IRCCs and SRCCs compare well with earlier reports. The better cancer-specific survival rate during the last period probably reflects the “stage migration” that has taken place between the first and last periods.

Women in Norway visit their physician more often than men. A survey published by Statistics Norway showed that women attended their physician 4.7 times per year, compared to 3.0 times per year for men (9). In the 1995 Health Survey published in the Official Statistics of Norway (8) it was shown that the total percentage of women who visited their general practitioner or practising specialist during the previous year was considerably higher than that for males. Even the figures for admittance to hospital were higher in the female group. The most probable explanation for the higher percentage of females in the IRCC group is that more visits to physicians lead to more imaging investigations. Studies from Japan, where ultrasound is a routine part of health examinations, demonstrate that IRCCs account for 66% of all RCCs (12). Greater use of diagnostic imaging results in the diagnosis of more IRCCs among females than males. Our data support this hypothesis. To our knowledge, no other reports on this topic have been published. Tsui et al. (2) described a tendency in the same direction as we do, whereas Lightfoot et al. (6) reported no such difference with regard to sex. Our series revealed a significantly ($p = 0.02$) higher proportion of low-stage (I–II) tumours in the female group. Logically, this is an implication of the higher percentage of IRCCs in this group. In contrast, we were not able to demonstrate a lower average tumour size in the female group. No other papers have been found on this subject.

Our survival data indicated a long-term benefit in the female group. This benefit was reported by McNichols et al. (18) in 1981, but no explanation for the phenomenon was given by the authors. Higher survival rates are to be expected in groups with a high

percentage of IRCCs. There was, however, no difference in survival between males and females in the IRCC group in our study (Fig. 4). In contrast, there was a tendency towards better survival among women in the SRCC group (Fig. 3). The data were not significant but a tendency towards lower TNM stage among females was present. Women probably respond earlier to symptoms of disease, and are less resistant to seeing physicians than men.

The results of the multivariate analysis showed that stage was the only independent prognostic factor. This is in line with a hypothesis, suggesting that regarding incidentally detected tumours, gender, operation period, the showed better survival rates is due to "stage migration".

As suggested by most recent studies, including this one, the more widespread use and enhanced quality of ultrasound, magnetic resonance imaging and CT is responsible for the increase in IRCC detection. Even easier access to these modalities in the years to come will probably increase the number of IRCCs still further. Prospective screening studies to define the incidence of IRCC in populations as well as a cost-benefit analysis with regard to survival are warranted.

CONCLUSION

The number of IRCCs is increasing, probably as a result of better and more widespread use of CT and ultrasound. IRCCs have lower TNM stage and are smaller than SRCCs. IRCCs are associated with better long-term cancer-specific survival than SRCCs, due to "stage migration". Probably as a result of greater use of the healthcare system, there is a higher percentage of females with IRCCs than would be expected from previously published epidemiological data. Women have more low-stage tumours at diagnosis and higher cancer-specific survival rates than men.

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