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Post Operative Radiotherapy Improves Disease Free But Not Overall Survival in High Risk Renal Cell Carcinoma Patients

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ABSTRACT

Purpose: To evaluate treatment outcome and the value of postoperative radiotherapy in treatment of patients with renal cell carcinoma (RCC).

Material and methods: The records of 136 radically treated RCC patients were revised. The patients were treated at the National Cancer Institute of Cairo and Kasr El-Aini Centre of Radiation Oncology and Nuclear Medicine of Cairo University between 1989 and 1997. According to the AJCC-TNM staging 21% had stage II, 36% had stage III and 43% had local stage IV disease. Seventy-eight patients received post-operative radiotherapy to the renal bed and the para-aortic lymph-nodes, while 58 patients did not .

Results: The 5-year over-all and disease-free survival estimate for the whole group were 49% (SE = ± 14%) and 23% (SE = ± 6%) respectively. Neither postoperative radiotherapy nor any of the tested potential prognostic factors have shown to have an impact on overall survival. The disease-free survival on the other hand, was significantly influenced by three variables namely; renal vein involvement (p = 0.006), capsular infiltration (p = 0.0003) and post-operative radiotherapy (p = 0.001). Post-operative radiotherapy improved the 5-year DFS from 17% (SE = ±5%) to 28% (SE = ± 9%) and increased the median DFS from 15 (SE = ± 5) months to 25 (SE = ±5) months. On multivariate analysis, capsular infiltration (p = 0.005) and post-operative radiotherapy (p = 0.01) remained to be significant independent parameters influencing disease-free survival. Adjuvant radiotherapy reduced the 5-year cumulative risk of local failure from 38% to 22% (p = 0.0145) but have no effect on the cumulative risk of developing distant metastasis.

Conclusion: This set of data supports the role of post-operative radiotherapy in improving the local control rate in locally advanced and high-risk RCC patients.

Key Words: *Renal cell carcinoma - Radiotherapy - Long tern results - Prognosis*

INTRODUCTION

A surgical resection is the accepted, often curable therapy for patients with non-metastatic renal cell carcinoma (RCC). A radical resection should include removal of the kidney, adrenal gland, perirenal fat and Gerota's fascia with or without regional lymph nodes dissection **[7,8,18-20]**. The effectiveness of lymphadenectomy has not been definitively proven, yet it is a mandatory procedure when preoperative assessment shows enlarged positive nodes **[15]**. Some retrospective studies showed survival benefit for adjuvant post-operative radiation therapy **[3,10,17, 22]**. However, this has not been confirmed in prospective randomised trials **[6,12,14]**. Because of the poor radiotherapy techniques and bad inclusion criteria in some of these trials, the value of postoperative external-beam radiation therapy is still debatable **[2]**.

We reviewed all files of patients with RCC that were treated in the National Cancer Institute (NCI) of Cairo and Kasr El-Aini Centre of Oncology and Nuclear Medicine (NEMROCK) between 1989 and 1997. Treatment outcome and various prognostic factors were analyzed with the aim of shedding some light on the value of postoperative radiotherapy in treatment of these patients.

PATIENTS AND METHODS

The records of 136 radically treated RCC patients were revised. Fifty seven patients with

distant metastases and/or inoperable advanced disease at diagnosis were excluded. Seventy-five patients were males and 61 were females, with male/female ratio of 1.2:1. Seventy-two patients had right-sided tumors and 64 patients had left sided tumors. The age ranged from 16 to 76 years with a median age of 54 years.

Based on the clinical, operative and pathological data in the files the patients were re-staged according to the most recent AJCC-TNM Cancer Staging Manual [**1**]. There were 26 patients with stage II, 44 patients with stage III, 53 patients with "local" stage IV and 13 patients without enough information to estimate stage. Patients characteristics according to the various prognostic factors are seen in Table (1).

Adjuvant systemic therapy was given to 15 patients. It was in the form of combination chemotherapy (Vinblastin, Bleomycin and Methotrexat) in 9 cases, hormonal treatment (Provera) in 4 cases and interferon in 2 cases.

Seventy-eight of the 136 patients received post-operative radiotherapy to the renal bed and the para-aortic lymph-nodes, while 58 patients did not. The criteria for giving postoperative radiotherapy were: positive surgical margin, capsular infiltration, high grade or sarcomatoid subtype and positive para-aortic nodes. However, because of the absence of standardized protocol, the decision to give postoperative radiotherapy was individualized and certain violations to these rules have occurred without clear explanations in the patients' files as to why this particular decision was taken. Table (2) shows the distribution of most important prognostic factors between those receiving and those not receiving post-operative radiotherapy.

Post-operative radiotherapy was given as conventional daily fractions of 1.8 to 2 Gy. Typically, in the first 40 to 44 Gy the target volume encompassed the nephrectomy bed, para-aortic lymph nodes and surgical clips by two-parallel opposing AP/PA fields using either Cobalt-60 machines or linear accelerators (6MV). Higher doses were given as "boosts" to smaller volumes including the renal bed and areas of microscopic or suspected residual (usually excluding the LNs). Boosts were given using multiple fields. Multiple-field arrangements and shaping, were individualized to minimize the dose to the normal bowel and liver. the median dose to the renal bed was 50 Gy (range; 24 to 60 Gy) and the median dose to the draining para-aortic lymph nodes was 42 Gy (range; 24 to 50 Gy).

CT scans or ultrasound of the abdomen was used in the preoperative assessment of all patients. Following the end of the local treatment, patients were evaluated every 1 to 2 months during the first 2 years then every 3 to 6 months thereafter. Abdominal imaging studies were ordered every 6 months on the average and chest X-ray every year. Bone scans were only ordered on suspicion of metastases.

A local failure was defined as failure that occurred within renal bed or in para-aortic nodes. A distant failure is that occurring outside the local area. Once a local recurrence is detected, the patient was routinely checked for distant metastases and vice versa. Therapy for failure was invariably palliative. The follow-up period ranged from 1 to 120 months with a median follow-up of 24 months. Thirty-one patients had completed 5 years of follow up.

Overall and disease-free survival data were calculated using the Kaplan-Meier product limit method [**11**]. All time-dependent outcome were calculated from the day of surgery and patients' data was censored where the outcome of interest had not yet occurred at last follow-up. Univariate analysis was performed, by generating survival curves for categorical variables and comparing curves using the logrank test. Continuous variables were divided at the median. A multivariate analysis of predictors of local and distant failure was generated using stepwise regression analysis and the cox proportional hazards model [**4**]. The cumulative risk of local failure was tested using the hazard function. Statistical software used was the SPSS for windows. The following parameters were considered to be potential predictors of outcome and were selected for univariate and subsequently multivariate analysis; age, sex, side, capsular infiltration, involvement of renal vein, lymphadenectomy, lymph node involvement, pathological subtype, AJCC-TNM stage and post-operative radiotherapy.

RESULTS

Excised tumour sizes ranged from 5 to 30 cm in greatest diameter, with a median of 10 cm. The pathology reports showed 47 patients to have renal cell carcinoma not otherwise spec-

ified. The next common pathological subtypes were the clear cell carcinoma subtype (46 cases), then the granular subtype (21 cases). Eight cases had a sarcomatoid type and 8 cases were reported as undifferentiated. Only 6 cases had a mixed clear and granular histology.

Following radical treatment, 10 patients developed local failure as a first event and 9 patients developed simultaneous local failure + distant metastases, while 54 patients developed distant metastases only. The following organs were the only sites of metastasis; lung (30%), bone (19%), liver (15.8%) and brain (4.2%). Other sites such as skin and distant lymph nodes were affected in 9.5% of metastatic cases. Multiple organ involvement was evident at first presentation of metastasis in 20.6% of metastatic cases.

Using the Kaplan Meier estimate, the 5-year over-all survival estimate for the whole group were 49% (SE = ±14%). The 5-year overall survival data according to stage were 55% for stage II (SE = ±12%) and 28% (SE = ±16%) for the combined stage III and local stage IV (p = 0.07). Non of the tested potential prognostic factors have shown a statistically significant impact on overall survival.

The 5-year disease free survival (DFS) estimate for the whole group was 23% (SE = ±6%) while he median DSF time was 22 months (SE = ±4). According to the AJCC-TNM stage the 5-year DFS were 35% and 11% for patients in stage II and the combined stage III and IV respectively. The univariate analysis using the log rank test has shown stage to affect DFS with a power very close to significance (p = 0.06). Three other variables had a significant impact on DFS namely; renal vein involvement, capsular infiltration and post-operative radiotherapy. As seen in Table (3) the 5-year DFS and the median survival results are worst in the group of patients with renal vein invasion or capsular infiltration. It also shows that postoperative radiotherapy improved DFS from 17% to 29% and increased the median DFS from 15 months to 25 months. Figs. (1,2 & 3) shows the DFS curves for the prognostic factors seen by univariate analysis to be of statistical significance.

In the multivariate analysis, only two variables proved to be significant independent parameters affecting DFS namely; capsular infiltration (p=0.005) & post-operative radiotherapy (0.01). These results are shown in Table (4).

The hazard function demonstrated that the value of adding postoperative radiotherapy was to decrease the risk of local failure. Postoperative radiotherapy decreased the 5-year cumulative risk of developing local failure from 38% to 22% (p = 0.0145). On the other hand, postoperative radiotherapy has failed to decrease the cumulative risk of developing distant failure by any significant proportion (p = 0.2254).

Table (1): Description of the patients' material according to the prevalence of the various tested prognostic factors.

Parameter	Yes	No	Unknown
Lymphadenectomy	104	18	14
Capsular infiltration	63	61	12
Stage III & (local) IV	97	26 (stage II)	13
Renal vein involvement	31	61	44
Positive nodes	37	60	39

Table (2): Patients' characteristics.

Variable	Post. Op. RTH (78 cases)	No RTH (58 cases)
Median age (years)	55	50
Male : female ratio	1.3-1	1.2-1
Rt: Lt ratio	1.1-1	1.1-1
Lymphadenectomy	68	36
	87%	62%
Renal vein involvement	22	9
	28%	14%
Positive LNs	23	14
	29%	24%
Capsular infiltration	43	20
	55%	34%
Positive surgical margin	3	2
	5%	4%
Pathological subtypes:		
• Clear cell	31 (40%)	15 (26%)
• Granular	10 (13%)	11 (19%)
• Mixed	4 (5%)	2 (3%)
• Sarcomatoid	4 (5%)	4 (7%)
• Undifferentiated	4 (5%)	4 (7%)
• Unspecified	25 (32%)	22 (38%)
Median T. size (cm)	10	10
Receiving adjuvant	10	5
Systemic treatment	(13%)	(9%)
AJCC-TNM stages:		
• II	12%	35.4%
• III	40%	31.3%
• IV	48%	33.3%

Table (3): The results of the kaplan meier and the log rank univariate analysis of the effect of various prognostic factors on disease free survival (DFS).

Variable	Yes		No		*p* value
	5-year DFS (±SE)	Median DFS (m) (± SE)	5-year DFS (±SE)	Median DFS (m) (± SE)	
Male sex	18% (6%)	15 (5)	21% (8%)	11 (5)	0.82
Rt side	17% (7%)	12 (3)	21% (7%)	16 (6)	0.98
Positive nodes	38% (9%)	23 (16)	31% (11%)	15 (11)	0.11
Stage	(II)		(III&IV)		
	35% (7%)	18 (6)	11% (7%)	11 (3)	0.06
Renal vein invasion	13% (8%)	12 (3)	42% (9%)	30 (13)	$p = 0.006$
Capsular infiltration	26.1% (8%)	10 (3)	36.2% (9%)	30 (12)	$p = 0.0003$
Postoperative radiotherapy	28% (9%)	25 (5)	17% (5%)	15 (4.8)	$p = 0.001$

Table (4): The results of the multivariate analysis for prognostic factors affecting disease free survival (DFS).

Variable	Multivariate anslysis	
	p-value	95% CI
Renal vein involvement	0.86	0.7 to 1.4
Capsular infiltration	0.005	0.3 to 0.8
Postoperative radiotherapy	0.01	1.1 to 3.2

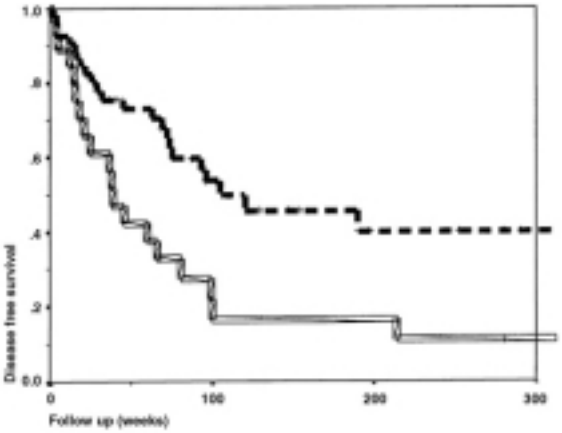

Fig. (2): Disease free survival for patients having positive renal vein involvement (solid line) and those without renal vein involvement (dashed line). The difference between the curves was statistically significant.

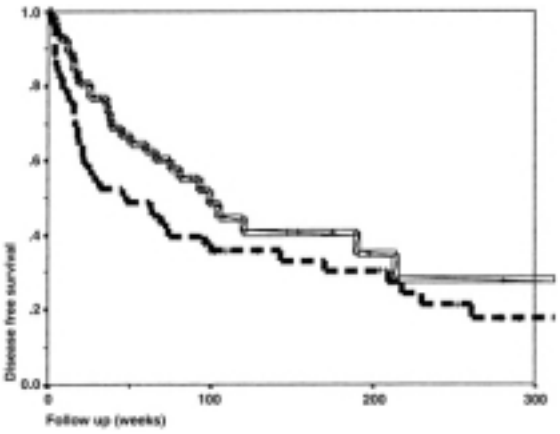

Fig. (1): Disease free survival of patients receiving postoperative radiotherapy (solid line) and those not receiving radiotherapy (dahed line). The difference between the curves was statistically significant.

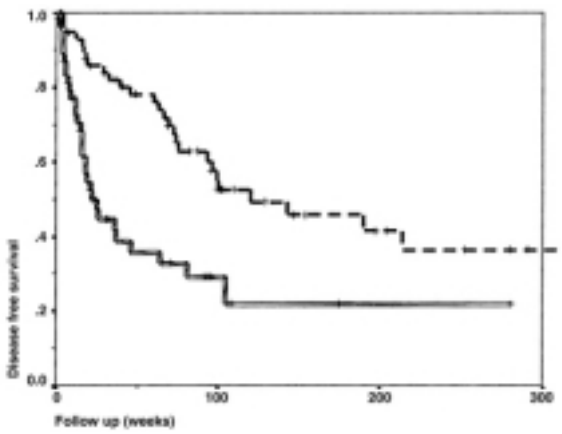

Fig. (3): Disease-free survival for patients having positive capsular infiltration (solid line) and those not having capsular infiltration (dashed line). The difference between the curves was statistically significant.

DISCUSSION

In RCC, the stage of the disease is believed to be the most important prognostic factor for survival. Literature data reveal a 5-year survival data around 60%, 44% and 10% for stage II, III and IV respectively [5,9,21]. Most of the literature data combines metastatic and locally advanced patients under "stage IV" category. In this report a substantial number of patients had a "local" stage IV and were treated radically with a curative intent using local measures only. We felt it is appropriate therefore to combine stage III and IV in the analysis of overall survival. Our 5-year overall survival data of 55% for stage II (SE = ±13%) and 28% (SE = ±17%) for the combined stage III and local stage IV, seemed to agree with the data in the literature. Though close to significance, this difference in the 5-year overall survival according to stage was not statistically significant. The reasons could be related to the short median follow up period and the unequal distribution of cases as most of the patients were of stage III and IV and only 26 patients were in stage II.

The role of lymphadenectomy is still a controversial issue. The great majority of patients in this study have undergone lymphadenectomy because of the advanced stage at diagnosis, which carried an increased risk of lymph-node involvement. The lack of detailed information on the operative procedure in the patients' files hampered the derivation of any solid conclusion regarding the value of lymphadenectomy in this study.

The prognostic significance of renal vein invasion has been the subject of considerable debate. A worse prognosis in patients with invasion of the renal vein was seen by some authors [16] and not by others [21]. In this study, the univariate analysis showed that both capsular infiltration, renal vein involvement did increase the risk of failure. It is important to note that renal vein invasion is often associated with capsular infiltration and perinephreic invasion of primary tumor. It was reported that patients with tumors only involving renal vein without perinephric fat invasion, the 5-year survival rate was 84% comparable to that of patients with stage I [9]. The multivariate analysis in this study seemed to verify that since it excluded renal vein invasion and kept capsular infiltration as an independent prognostic factor with high power of statistical significance ($p = 0.005$).

Despite the encouraging results of early retrospective studies [3,17], prospective trials have failed to demonstrate an advantage to patients receiving radiation therapy after surgery. Finney (1973) showed that postoperative radiotherapy did not influence the incidence of locoregional failure or distant metastasis. Instead, radiation had deleterious effects on survival as a considerable number of cases receiving radiotherapy died from coincidental causes, including radiation liver damage [6]. The Copenhagen RCC study group randomised 72 stage II & III patients between 1972 to 1984 to receive or not post-operative radiotherapy following radical nephrectomy. No difference could be demonstrated between patients who received postoperative radiotherapy and those who did not [12]. The same was shown in the retrospective studies by Peeling et al. [14]. The lack of benefit from postoperative irradiation in the prospective trials may be explained by poor patient selection and radiation therapy techniques. Aref et al. [2] also believed that the high incidence of distant metastases and paucity of local failure might explain the failure of radiotherapy to improve the survival results in these trials. It was thus suggested that if benefit from postoperative radiotherapy exists it would be demonstrable only in patients with high-risk features that would increase their risk of local failure. At least 3 recent retrospective studies have shown improved local control rate after postoperative radiotherapy in locally advanced RCC patients compared to no radiotherapy group. Kao et al., in a retrospective series of 12 patients with high risk locally advances tumours with perinephreic invasion or surgically positive margins had demonstrated a 100% local control rate with postoperative irradiation. The 5-year local failure rate was 30% in a comparable group of patients treated by surgery only during the same period ($p < 0.01$) [10]. Another retrospective study demonstrated that patients with T3 tumors had a statistically significant lower local failure rate (10%) when given post operative radiotherapy compared to similar patients undergoing nephrectomy alone (37%) [22]. A Polish study of 186 patients showed that the median time to relapse for local or distant metastases were approximately two times longer in patients with adjuvant radiotherapy compared to those without [13]. In agreement with these reports, this study showed that postoperative radiotherapy significantly reduced the cumulative 5-year local failure rate from 38% to 22% (p =

0.0145). The relatively high rate of local failure reported in this study is due to: the very advanced tumors and to the use of the cumulative risk of failure as a method of analysis. Table (2) showed that the group of patients receiving postoperative radiotherapy was of poorer prognosis and at higher risk of failure since 88% of the patients were stage III and local stage IV. Consequently, they also had a higher percentage of positive renal vein invasion, capsular infiltration and positive surgical margin. The improvement of disease-free survival in this group despite all these high-risk factors could be used to confirm the value of the of adjuvant postoperative radiotherapy in high-risk RCC patients. The improvement in DFS has to be weighed against the risk of radiation-induced complication. Unfortunately, as this was not a prospective study there was not enough data in the patients' files to give a clear view on radiation-induced complication rate. However, with the use of CT planning and modern techniques, it was shown that radiation can be delivered to the renal bed without undue morbidity and with a low and acceptable complication rate [**10**].

We conclude that giving post-operative radiotherapy in high-risk patients with RCC is justified. It should be given with the aim of improving disease free survival. The improvement in disease free survival seems to be through improvement of the local control rate.

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