Pelvic Radiotherapy after Renal Transplantation

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Abstract. *Background: After renal transplantation, patients have a higher incidence of developing cancer necessitating pelvic radiotherapy, but there is a lack of data for such therapy in this patient group. Patients and Methods: Nine patients with pelvic renal transplants were treated with pelvic radiotherapy between 04/2002 and 06/2011. Treatment was carried out for prostate (n=4), rectal (n=2), and anal cancer (n=1), osseous metastasis (n=1), and Hodgkin's disease (n=1). The mean age of the transplants was 12.6 years. Results: The mean total dose to the target volume was 60.2 Gy, the mean maximum dose to the transplant was 10.0 Gy, with a mean dose of 2.1 Gy. The mean creatinine clearance before start of radiotherapy was 48.9 ml/min. After a mean follow-up of 23 months, no patient showed failure of the transplant and the mean creatinine clearance was 64.2 ml/min. Conclusion: Using modern radiotherapy techniques, low doses to the transplant can be achieved without compromising target treatment and without transplant failure. A mean dose of <4 Gy seems to be well-tolerated by the graft.*

Renal transplantation is the treatment of choice for most patients with end-stage kidney disease (1, 2). Due to improvements in immunosuppressive therapy, with the introduction of newer agents, both patients with renal transplants but also those with grafts have a longer probability of survival, with a reduced incidence of acute rejection episodes of <10% (3). Today the main problems are related to the adverse events of prolonged immunosuppression, including cardiovascular disease, infection and malignancy; in addition, the age of patients is one of the most important risk factors for carcinogenesis (4). Cancer in patients with renal transplantation mostly includes skin cancer and lymphoproliferative disorders, but the development of the solid tumours as well (5-8). One therapeutic oncological option for patients with pelvic malignancies is radiotherapy (9-11). However, the anatomical position of the graft in the pelvis can be very challenging for radiotherapy administration. There are only few series in the literature describing pelvic radiotherapy for renal transplantation patients, and there is a lack of data regarding the dose that the renal transplant may tolerate without impairment of its function.

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Patients and Methods

This retrospective analysis included all patients (male: n=7, female: n=2) with a renal transplant in the pelvis who had been treated with pelvic radiotherapy between 04/2002 and 06/2011. For all the patients, a three-dimensional (CT)-based conformal treatment planning and technique was performed with a single dose of 1.8 or 2.0. Both the target volume and the organs at risk including the renal transplant had been outlined to calculate the dose and the dose- volume histograms. No patient underwent simultaneous chemotherapy. Radiotherapy used photon energies of 6, 10 and 23 MV delivered with a linear accelerator with individual field collimation. The total dose was dependent on the underlying malignant disease. Before, during and after the treatment, constant nephrological testing was carried out. For all patients, a close follow-up was performed regarding the function of the renal transplant. Graft function was monitored by serum creatinine levels, creatinine clearance and serum levels of urea. The further course of disease was assessed by regular visits to our outpatient clinic.

Results

The mean age of the patients at the time of radiotherapy was 65.8 years (range=48-75 years), the mean age of the renal transplant was 12.6 years (range=1-18 years). Treatment was carried out for prostate cancer (n=4), rectal cancer (n=2), anal canal cancer (n=1), pelvic osseous metastasis of prostate cancer (n=1) and Hodgkin's disease (n=1). The mean total dose to the target volume was 60.2 Gy (range=30.0-73.8 Gy) with a mean single dose of 1.8 Gy (range=1.8-2.0 Gy). The mean maximum dose to the renal transplant was 10.0 Gy (range=0-32.2 Gy), with a mean dose of 2.1 Gy (range=0.1-6.4 Gy). The mean creatinine clearance before the start of radiotherapy was 48.9 ml/min (range=21-87 ml/min), the mean serum creatinine level was 114.7 μmol/l (range=62-185 μmol/l), and the mean level of urea was 15.0 mmol/l (range=4-34 mmol/l). After a mean follow-up of 23 months

(3-63 months), five patients showed no evidence of tumour relapse; two patients developed a carcinoma *in situ* and an invasive carcinoma of the bladder, respectively; one patient developed local recurrent disease with metastatic spread; and the patient irradiated for pelvic osseous metastasis developed metastatic spread in other regions. In two patients, re-irradiation was carried out for local recurrent rectal cancer (patient 7) and for newly-developed bladder cancer (patient 3) after a time interval of 13.4 and 41.5 months, respectively, with a total dose to the planned target volume (PTV) of 30.6 Gy and 24 Gy, a maximum dose to the transplant of 1.87 Gy and 12.9 Gy, and a mean dose to the transplant of 0.34 Gy and 1.0 Gy, respectively. Four patients died, out of which three died due to cancer and one patient due to other causes. No patient experienced a failure of the transplant, with a mean stable creatinine clearance of 64.2 ml/min (range=25-171 ml/min), a mean serum creatinine level of 113.2 μmol/l (range=74-175 μmol/l) and a mean serum urea level of 16.9 mmol/l (range=5.4-31.3 mmol/l) (Table I).

Discussion

Organ transplantation is associated with significant short-term complications, such as rejection and infection. However, the results of kidney transplantation regarding the graft, as well as patient survival, have improved over the past decades, mainly due to the introduction of new immunosuppressive therapies. Nowadays, special focus is on the long-term outcome. Some immunosuppressive drugs are associated with an increased risk of cancer which is of higher incidence in the transplant population than in the general population. Therefore, the development of cancer has been shown not to be such a rare complication in this cohort of patients (12-14). A post-transplant malignancy was shown to be the third most common cause of death in renal transplant patients (15, 16). Particularly in patients after kidney transplantation, there is an increased risk by up to 20-fold of lymphoma and by up to two-fold of solid cancer such as prostate cancer (7, 17, 18). However, due to better long-term outcomes with improved patient survival on the one hand, and due to the possibility of transplantation in older patients on the other, the incidence of post-transplant malignancy may even rise. There is evidence that the risk for developing cancer increases with age and long-lasting immunosuppressive medication due to disturbances of the immune system (5-8). The immunosuppressive treatment may support oncogenesis caused by certain viruses, which alter the surveillance of neoplastic cells leading to impaired DNA repair mechanisms and DNA damage (15, 17, 19). However, a definitive explanation is still unknown. On the other hand, patients with transplants are examined more often and more intensively, meaning that malignant disease will be detected earlier and more often in this cohort of patients (20). There are only few reports in the literature dealing with pelvic radiotherapy for patients with a renal transplant in the pelvis. The oncological treatment should take into account the preservation of graft function on the one hand, and possible chance of cure from cancer on the other. External beam radiotherapy is a frequently used treatment option for patients with pelvic malignancies, as a possibility for a non-invasive therapy that is generally well-tolerated. However, the aim of radiotherapy is to deliver a high volume dose to the target, including the tumour, and to avoid damage to the normal tissue, implementing the concept of tolerance-doses of organs at risk. Emami *et al*. were one of the first to define limits for various organs (21). In 2010, the tolerance doses of the kidneys were redefined by Marks *et al*. (22). A clinically-relevant renal dysfunction with a probability of <5 % can be started if the mean dose to both kidneys is <15-18 Gy and of <50% in cases of a mean dose of <28 Gy. In cases of radiation nephropathy, structural features include mesangiolysis, sclerosis, tubular atrophy, and tubulointerstitial scarring, leading to loss of the organ function (23). Kal *et al*. demonstrated that in patients with total-body irradiation as part of the conditioning regimen for hematopoietic stem cell transplantation, a total dose of >16 Gy can lead to an increase of the frequency of dysfunction (24, 25). Linsenmeier *et al*. detected slight glomerular nephritis in three out of 32 paediatric patients treated with total-body irradiation with a total dose of 12 Gy (26). However, Bölling *et al*. found a cumulative incidence of kidney toxicity of 25 % in 270 patients undergoing total-body irradiation with total doses ranging from 4-12 Gy (27). However, the tolerance dose for a transplanted organ in patients exposed to immunosuppression may be much lower. Therefore the renal transplant should be exposed to as low a dose as possible on the one hand, but without compromising that to the target volume on the other, in order to obtain a high cure rate. In the literature, there are only case reports or small series regarding this patient cohort. Konety *et al*. reported on 18 patients with prostate cancer and a renal transplant graft of whom three were treated with radiotherapy with a mean dose of 65 Gy to the target volume and with shielding of the graft (28). Two patients were alive, while one patient died due to other causes. However, the authors did not give details of the exposure, nor on the functioning of the graft. Therefore they only demonstrated the feasibility of the radiotherapy for this cohort of patients. Mouzin *et al*. described the outcome of eight patients with renal grafts and prostate cancer treated with radiotherapy (29). After a median follow-up of 28 months, two patients had local relapse, two patients died from causes other than cancer, and four patients were alive and free of local recurrence. In seven patients, the function of the renal allograft was unimpaired, while one patient experienced renal failure three months after the end of the radiotherapy due to terminal chronic rejection. The dose delivered to less than 10 % of the graft was 2 Gy in one patient, <5 Gy in five patients (including the patient with chronic rejection), 11 Gy in one patient and 13 Gy in one

Table I. *Clinical characteristics of the patients.*

Patient	Gender	Age (years)	Diagnosis	Max dose PTV (Gy)	Transplant dose (Gy)		Creatinine clearance (ml/min)	
					Maximum	Mean	Before RT	After RT
1	m	72	Prostate cancer	66.6	1.9	1.3	21	27
2	m	72	Prostate cancer	73.8	0.61	0.22	46	38
3	f	64	Anal canal cancer	60	23.26	3.78	68	56
4	m	67	Prostate cancer	72	2.01	0.61	68	75
5	m	75	Osseous metastasis of prostate cancer	66.6	17.07	2.3	23	25
6	m	67	Prostate cancer	72	3.47	0.84	26	35
7	f	64	Rectal cancer	50.4	32.23	6.39	46	81
8	m	64	Rectal cancer	50.4	9.07	3.22	87	171
9	m	48	Hodgkin's disease	30	0.04	0.14	55	70

PTV: Planning target volume, RT: radiotherapy.

patient, and therefore below the tolerance dose that is reported for otherwise healthy patients with functioning kidneys. Detti *et al*. reported a single case with prostate cancer irradiated with a total dose of 70.2 Gy to the target volume, a maximum dose to the graft of 1.88 Gy and a mean dose to the graft of 0.36 Gy, without any impairment of the graft function during further follow-up (30). However, radiotherapy can also be used in patients with acute renal allograft rejection. In this setting, a total dose of 6 Gy with single doses of 1.5-2.0 Gy were applied to the whole kidney, with up to 100 % renal graft salvage (31). In our cohort of patients, we saw no graft failure with impairment of renal function; no patient had to return to dialysis due to transplant failure. The applied mean doses to the kidney were less than 4 Gy in all but one patient, which is clearly below the tolerance dose given by Marks *et al*. and lower than the dose range of 4-12 Gy reported by Bölling *et al*. in patients undergoing total-body irradiation.

To conclude, pelvic radiotherapy is feasible for this special cohort of patients by the use of three-dimensional conformal radiotherapy with adequate covering of the target volume while sparing the organs at risk, including the graft. A mean dose of <4 Gy seems to be well-tolerated by the graft.

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