Intraoperative Radiotherapy for Locally Advanced Prostate Cancer: Treatment Technique and Ultrasound-based Analysis of Dose Distribution

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Abstract. *Background: To present the technique and dose distribution of intraoperative radiotherapy (IORT) for prostate cancer. Patients and Methods: Pelvic lymphadenectomy, prostate IORT and radical retropubic prostatectomy was performed in 11 prostate cancer patients. Prostate thickness and rectum depth were measured with intraoperative ultrasound. IORT was delivered by a mobile linear accelerator in the operating room (electron beam, 12 Gy at 90% isodose). Results: The mean preoperative probability of organ-confined disease was 10% (Memorial Sloan Kettering Cancer Center nomograms). Mean prostate thickness, width and length were 3.4 cm, 4.6 and 4.9 cm, respectively. Mean rectum depth was 3.3 cm. Mean doses to the posterior prostate capsule, 5-mm lateral prostate margins and at the subsequent uretheral stump area were 4.6 Gy, 8.7 Gy and 11.3 Gy, respectively. Maximum mean rectal dose was 4.9 Gy. Conclusion: IORT appeared a feasible approach for prostate cancer, showing a satisfactory dose coverage to the prostate bed with relatively low rectal dose. However, high variability in dose distribution calls for further study of patient selection criteria and dosimetry.*

Radical prostatectomy is a well-accepted treatment for prostate cancer (1). Several retrospective series and two recent large randomized trials demonstrated an improved biochemical and clinical progression-free survival in patients with positive margins or pT3 treated with postoperative radiotherapy (2-4). External beam postoperative irradiation (EBRT) consists of a seven week schedule and may be correlated with significant side-effects. Moreover, the geometric uncertainties in defining the target area and organ motion issues may jeopardize the benefit of postoperative radiotherapy (5). Alternative approaches are being sought. Intraoperative radiotherapy (IORT), usually combined with EBRT, has been used for many years for various locally advanced tumors (6). This approach offers several radiobiological, physical and clinical advantages. Recently, IORT using an electron beam (IOERT) has been proposed prospectively at the European Institute of Oncology, Milan, Italy, for intermediate- and high-risk prostate cancer patients, candidates for radical prostatectomy. The aim of our study was to present this IOERT technique and to analyze its dose distribution. Toxicity as well as tumor control data will be the subject of a future report when longer follow-up data are available.

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Patients and Methods

Inclusion criteria. The inclusion criteria were as follows: recommended age <70 years, good performance status with no clinically relevant co-morbidities, biopsy-confirmed intermediate- or high-risk cN0 cM0 prostate adenocarcinoma (7), preoperative probability of organ-confined disease ≤25% (according to the Memorial Sloan Kettering Cancer Center nomograms) (8), patient preference for surgical therapy and written informed consent for IOERT. Endocrine therapy was permitted.

Treatment protocol. Diagnostic and staging procedures included transrectal ultrasound (TRUS)-guided biopsy confirming prostate adenocarcinoma, chest X-ray, bone scan, abdomino-pelvic computed tomography (CT) or magnetic resonance imaging (MRI), clinical evaluation (with digital rectal examination) and

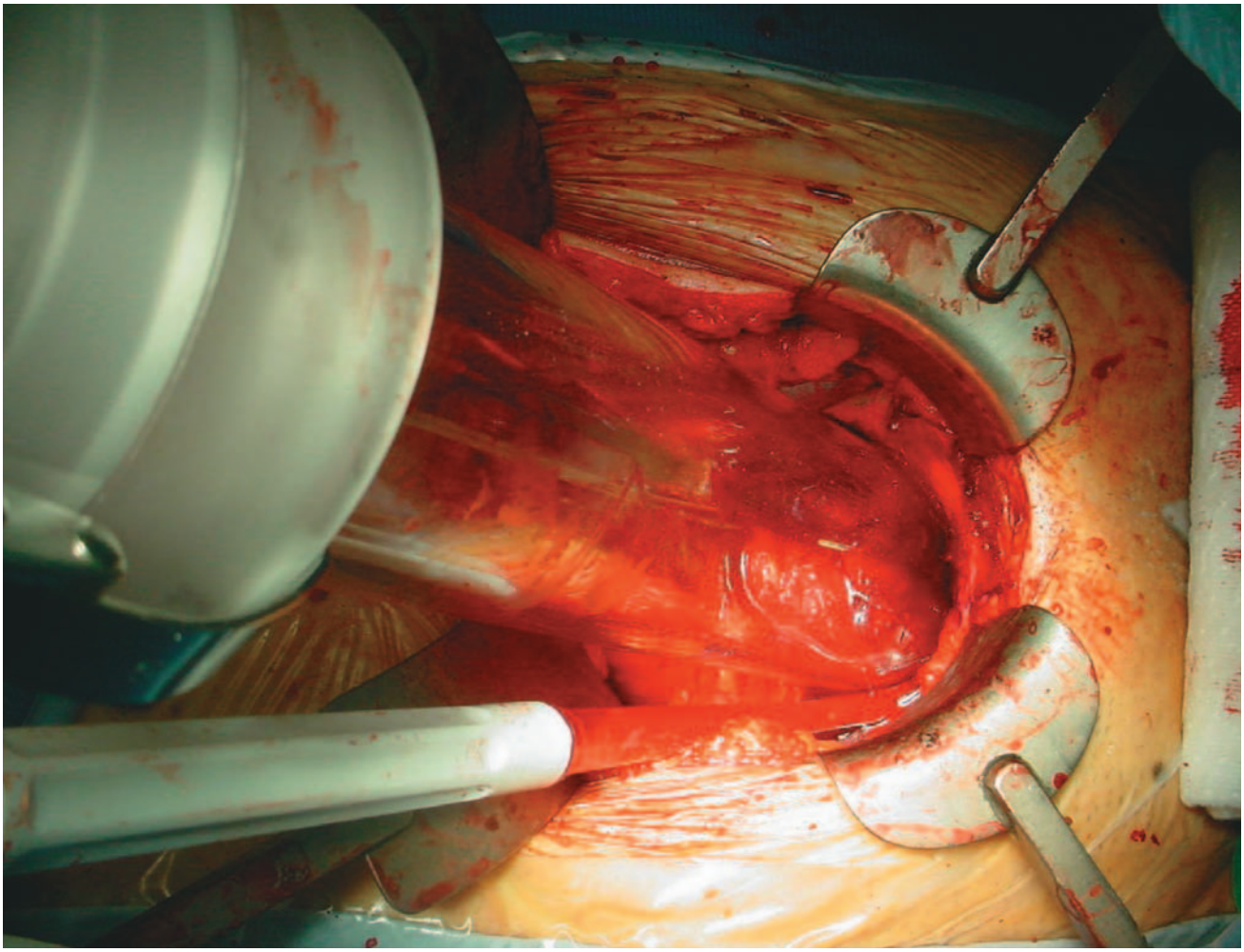

Figure 1. *The irradiated area as seen after positioning of the cylindrical applicator.*

blood biochemistry. All cases were discussed on a multidisciplinary basis. Patients were then examined by a radiation oncologist for a pre-planning evaluation, with pelvic CT and TRUS, and written informed consent was obtained.

For the surgery, the patients were put in the supine position. After pelvic lymphadenectomy, the IOERT field was prepared by starting the anatomical radical prostatectomy according to the Walsh technique (9-10) Four long wire landmarks of the lateral prostate pedicles, apex and bladder neck were inserted through and inside the perspex IOERT applicator. In this way, the whole prostate could be included in the irradiation field. Immediately before IOERT, transaxial and midsagittal ultrasound (US) images were acquired (SSD-2000, ALOKA, Tokyo, Japan). The prostate dimensions and rectum depth were measured in order to properly select the beam energy and applicator size (depth dose distribution had been determined in a water phantom during the commissioning of the treatment unit). IOERT was performed using a Liac (Info&Tech, Rome, Italy) mobile linear accelerator, working in the operating room. Liac was installed at our Institute in 2004 and is mostly used for partial breast irradiation (11). It can deliver electron beams with nominal energies of 4, 6, 8 or 10 MeV at a very high pulse dose (12-13). Beams are collimated by perspex applicators (Figure 1), flat-ended or beveled (15˚, 30˚, 45˚), with an inner diameter ranging from 3 to 12 cm; the nominal source to skin distance is 60 cm. The prescribed IOERT dose was 12 Gy at 90% isodose equivalent to the normalized total dose (NTD) of 46.3 Gy and 32 Gy calculated with a linear-quadratic formula, using an α/β ratio of 1.5 Gy and 4 Gy, respectively (14-15). Such a prescription was derived from our experience in IOERT as a boost for early-stage breast cancer (13). Similar doses are prescribed in other tumors (*e.g.* pancreatic, rectal cancers) treated with IOERT boost (6). After the IOERT, the prostatectomy was completed and the specimen was removed.

Postoperative EBRT at a dose of 45 Gy in 25 fractions was prescribed to the prostatic bed alone and the whole pelvis in case of pT3-4pN0 and pN1 disease, respectively, and scheduled three months after surgery.

Table I. *Preoperative patient and tumour characteristics, postoperative findings.*

Characteristic	
Number of patients	11
Age (years)	61 (range: 54-71)
Clinical stage:	
T2	5
T3	6
Biopsy based Gleason score	
Mean	7.3
Range	6-9
Initial PSA (ng/ml)	20 (range: 6.87-55)
Neoadjuvant endocrine therapy	
Yes	3
No	8
Preoperative nomograms, mean (range)*	
Organ confined disease	10% (1-25%)
Extracapsular disease	39.5% (17-57%)
Seminal vesicles involvement	26% (11-40%)
Lymph node involvement	24% (9-37%)
Initial risk category**	
Intermediate	2
High	9
Postoperative findings:	
Postoperative Gleason score	
Mean	7.6
Range	6-9
Pathological stage	
pT2 pN0	3
pT2 pN1	1
pT3 pN0	3
pT3 pN1	3
pT4 pN1	1
Upstaging	4
Downstaging	1
No change	6
Acute toxicity of EBRT (RTOG criteria) (30)	
Genitourinary	
0	0
1°	7
2°	1
Gastrointestinal	
0	6
1°	1
2°	1

PSA, prostate-specific antigen; *according to the Memorial Sloan Kettering nomograms (8); **according to D'Amico *et al.* (7); EBRT, external beam radiotherapy; RTOG, Radiation Therapy Oncology Group.

Results

Patient and tumor characteristics. Between June 2005 and December 2005, 11 prostate cancer patients were included in the study (Table I).

Table II. *Preoperative and intraoperative prostate and rectum measurements.*

	Preoperative TRUS-based measurement	Preoperative CT-based measurement	Intraoperative US measurement
Prostate thickness (cm)			
Mean	3.1	3.4	3.4
Range	2.2-4.3	2.3-4.6	2.5-4.8
Prostate width (cm)			
Mean	4.9	4.8	4.6
Range	3.4-6.2	3.2-6.2	3.4-5.6
Prostate length (cm)			
Mean	4.2	4.5	4.9
Range	3.7-5.0	3.8-5.7	4.1-6.0
Prostate volume* (cc)			
Mean	35.3	41.4	40.7
Range	14.7-59.2	17.9-71.2	22.2-67.2
Rectal depth (cm)	Not evaluable	Not evaluable	
Mean			3.3
Range			2.5-4.4

TRUS, transrectal ultrasound; CT, computed tomography; US, ultrasound; *prostate volume calculation= thickness x width x length x 0.532 (16).

Intraoperative organ measurements. Mean prostate thickness, width and length were 3.4 cm, 4.6 and 4.9 cm, respectively (Table II). Close agreement between the intraoperative US-based and the preoperative TRUS- and CT-based prostate measurements was found (16), showing that the latter imaging can be used *a priori* as a reliable indicator of the feasibility of IOERT for each individual patient.

Dosimetry analysis. The maximum available electron energy (10 MeV) was used in ten cases (91%). Eight MeV energy was selected in one case, where the prostate thickness was limited (2.5 cm). The applicator size of 5, 6 and 7 cm diameter was used in two, six and three patients, respectively. A thirty degree bevel angle was chosen in all cases, except one, where the 45° angle was preferred for better conformity to the surgical bed (avoiding the obstacle represented by the pubic arc).

Mean doses to the posterior prostate capsule, lateral prostate margins (at a distance of 5 mm) and areas corresponding to the future uretheral stump were 4.6 Gy, 8.7 Gy and 11.3 Gy, respectively (Table III). Maximum rectal dose was 4.9 Gy as an average. The urinary bladder (in particular the bladder neck) had to be partially included in the treatment field, thus receiving the whole prescribed dose in some areas.

We are aware that the linear-quadratic radiobiological model has not yet been demonstrated to be valid for a single high dose, however, no established alternative is available in the literature. Therefore, NTD (normalized total dose) and

BED (biologically equivalent dose) calculations using the linear-quadratic model are reported in Table III (17).

Postoperative findings. Organ-confined disease (pT2 pN0) was found in three patients (27%) (Table I). The mean number of the examined lymph nodes was 16 (range: 8-34). Seminal vesicle involvement, positive and close surgical margins were found in three, three and two patients, respectively, and peri-neural and vascular invasion in ten and two cases, respectively. Based on the definitive histological report, postoperative pelvic and prostatic bed EBRT was prescribed in five and three patients, respectively. Adjuvant endocrine therapy was proposed for seven patients.

Early postoperative complications (occurring within 30 days after hospital discharge) included significant and symptomatic lymphocele requiring percutaneous catheter drainage in one patient and prolonged catheterization (>14 days) due to a persistent anastomotic leakage in 3 patients. No patient developed acute urinary retention after catheter removal. The median estimated blood loss was 1000 ml (range, 200-3000 ml) requiring blood transfusion in four patients.

Table III. *Dosimetry results, normalized total doses and biologically equivalent doses [see text for explanation (14-15, 17)].*

Dose	NTD (Gy)	BED (Gy)
Prostate prescribed dose 12 Gy at 90% isodose (*i.e.* 13.3 Gy at the depth of dose maximum)		
α/β=1.5 Gy	56.2	131.2
α/β=4 Gy	38.3	57.5
Mean posterior prostate capsule dose 4.6 Gy (range: 0.6-8.4 Gy)		
α/β=1.5 Gy	8.0	18.7
α/β=4 Gy	6.6	9.9
Mean lateral prostate margin dose (+ 5 mm) 8.7 Gy (range: 2.4-12.0 Gy)		
α/β=1.5 Gy	25.4	59.2
α/β=4 Gy	18.4	27.6
Mean urethral stump dose 11.3 Gy (range: 6.0-12.0 Gy)		
α/β=1.5 Gy	41.3	96.4
α/β=4 Gy	28.8	43.2
Mean maximum rectal wall dose 4.9 Gy (range: 0.6-8.4 Gy)		
α/β=4 Gy	7.3	10.9
α/β=10 Gy	6.1	7.3
Maximum urinary bladder dose 13.3 Gy		
α/β=5 Gy	34.8	48.7

NTD, normalized total dose; BED, biologically equivalent dose.

Discussion

To our knowledge, our investigation represents one of the first extensive reports on the use of IORT for prostate cancer. Only early reports from two Japanese institutions (18-21) and data published exclusively in an abstract form (22) are available in the English language literature. In the early Japanese reports, a transperineal approach was used and the prostate was not removed after the procedure (18, 20). The transperineal approach has many disadvantages (high risk of rectal damage, no lymph node approach and a long lasting perineal discomfort to the patient) and therefore has been abandoned (21). More recently, at the Regina Elena Institute, Rome, Italy, IOERT (22 Gy) over the anastomotic site has been proposed after prostatectomy reconstruction (22). In our series, IOERT was proposed as an anticipated boost to the prostate bed to the dose of 12 Gy (performed before the prostate removal). The rationale for such a technique was to intraoperatively irradiate the whole surgical bed (approximately 5 mm around the prostate), while sparing the rectum as much as possible. In most cases, both endpoints were satisfactorily achieved, however high variability in the target and rectal doses was observed for each individual patient and between patients. This can be partially explained by the non-uniform thickness of the target and electron beam dosimetry. The clinical relevance of these well-known limitations of IOERT has not yet been established (6). Better dosimetric results could be obtained if more rigid patient selection criteria are used. For example, based on the preoperative CT measurements, cases showing a prostate wider than 5 cm or thicker than 3.5 cm (approximately 40% of depth dose for 10 MeV electron beams and 30° bevel angle applicator) should be excluded. In this context, the availability of higher electron energies could be helpful (23). A completely different approach could consist of IOERT following (instead of before) the prostatectomy, however such a procedure could lead to a significant increase in the rectal dose. An intraoperative US-based treatment planning system and *in vivo* dosimetry (using real-time micro-MOSFET detectors) could be helpful (12).

In our protocol IOERT was used as an anticipated boost, and prostatic bed or pelvic EBRT was scheduled three months after the surgery for all locally advanced patients (pT3-4 or pN1, respectively). The prescribed IOERT dose of 12 Gy at the 90% isodose is equivalent to the normalized dose of 56.2 Gy (α/β ratio 1.5 Gy) (14-15). The mean dose delivered to the prostate bed was 8.7 Gy which is equivalent to 25.4 Gy given with a conventionally fractionated regimen. Therefore, the sum of 45 Gy prescribed postoperatively and 25 Gy given intraoperatively is comparable to the doses prescribed for

postoperative EBRT (60-66 Gy) (2-3). However, these calculations should be interpreted cautiously, since the data on the radiation response of prostate cancer and late tissue responses are not yet clear (14-15, 24). Importantly, there are numerous data demonstrating the high sensitivity of prostate cancer cells to the fraction size (low α/β ratio) (14-15). In consequence, a high dose per fraction, as given with IOERT, should potentially lead to a therapeutic gain. This gain would be even more pronounced if the prostate cancer α/β ratio is lower than that of the late responding tissues (14, 24).

Future IOERT protocol modifications are considered. In particular, precise information on the lymph node status could allow two different therapeutic approaches. In those patients with lymph node metastases, prostate IOERT could be delivered as an anticipated boost followed by EBRT to the pelvis. In pN0 patients, IOERT could be delivered as an exclusive adjuvant radiotherapy, obviously up to a higher dose than that prescribed in the current protocol (such IOERT dose escalation requires further optimization of rectal dosimetry and shielding). Once the feasibility of IOERT is demonstrated, the equivalence of exclusive IOERT and postoperative seven-week irradiation should be studied in controlled prospective trials (as is already ongoing in breast cancer) (6). The results of such trials, if the equivalence of the two modalities is shown, might have important impact on radiotherapy logistic and economic aspects, as well as on the patient's convenience.

No further EBRT was proposed in our protocol for the pT2 pN0 patients with clear surgical margins (three out of 11 cases). The benefit of any adjuvant radiotherapy in this population has not been established. Therefore, to avoid potential overtreatment (adjuvant IOERT in low stage cancer), a more reliable preoperative staging and nomogram cut-off level should be used. Routine preoperative pelvic and/or endorectal coil MRI could be useful (25). Moreover, the probability of pathologically organ-confined disease should be low (for example, less than 10% instead of 25% used in the present study) (8). More recent nomograms on specific prediction of extracapsular extension may also be useful (26). Ideally, the best candidates for IOERT would be those patients with pT3 pN0 disease, for which the addition of radiotherapy after surgery improves outcome (2-4). The role of adjuvant radiotherapy in other patient populations (pT2 pN0, pT4pN0 or any pN1 cases) is not yet clear.

Since our study was planned to test the feasibility and technical aspects of IOERT, hormonal manipulation was permitted. This can make an accurate evaluation of the pathological specimen difficult (due to possible downstaging), as can be the assessment of the clinical outcome in short/medium terms (27). Future study on the use of IOERT in prostate cancer should therefore include well-defined criteria for hormonal treatment. Another critical aspect of any combined treatment is timing. In our study, postoperative EBRT was scheduled three months after surgery, corresponding to the recovery from surgery and the absence of major voiding problems (2-3). From the radiobiological point of view, such a time gap may reduce the efficacy and this aspect should be addressed in future IOERT studies. Importantly, the impact of IOERT on the peri- and early postoperative complication rate seems negligible. Indeed, both the rate of lymphocoele and blood loss data remain similar as in the reports on large series treated with prostatectomy and lymphoadenectomy without IOERT (28-29).

Conclusion

Our pilot study showed that IOERT delivered immediately before prostatectomy appeared a feasible approach for locally advanced prostate cancer, leading to a satisfactory dose coverage to the prostate bed with relatively low rectal dose. However, the high variability in dose distribution calls for further study on better patient selection and dosimetry. Careful analysis of the clinical outcome is warranted to define the role of IOERT in prostate cancer.

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