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Radiotherapy and Oncology 57 (2000) 315–321

 RADIO THERAPY
& ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR
THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer

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Received 18 September 2000; accepted 27 September 2000

Keywords: Seed implantation; Prostate cancer; Gleason score

1. Introduction

The last few years has seen an enormous increase in interest in the role of new transrectal ultrasound and template guided techniques for brachytherapy in localized prostate cancer. In the USA there has been a dramatic rise in the number of implants performed in the last 5 years. A similar rapid expansion is expected in Europe and this guidance is intended to indicate to those embarking on brachytherapy the factors which may be related to successful outcomes.

Brachytherapy to the prostate can be delivered either with permanent seed implants or with removable implants which are often delivered at high dose rate with iridium wire. The indications and techniques are different and these recommendations concentrate on permanent seed implants alone.

There have not been any randomized trials which compare prostate brachytherapy with other interventions for localized prostate cancer and the evidence that supports the recommendations comes from observational studies and consensus about what constitutes good practice. The guidelines have been written by a small working group of radiation oncologists, urologists and physicists on behalf of the ESTRO/EAU Urological Brachytherapy Group and the EORTC Radiotherapy Group

1.1. Patient selection

There are two aspects to patient selection. One is to identify

patients who are likely to have a good outcome in terms of biochemical disease free survival and the other to identify patients who will have a good functional outcome. The most significant prognostic factors for disease free survival are initial prostate-specific antigen (PSA), Gleason score and stage. For functional outcome the initial prostate volume and lower urinary tract symptoms best characterized by the International Prostate Symptom Score (IPSS) score provide the best guide to outcome.

1.2. Pre-treatment investigations

All patients should have a history and general physical examination to assess their suitability and fitness for brachytherapy. Digital rectal examination should be performed to indicate clinical stage. Sexual potency and lower urinary tract symptoms should be assessed with validated questionnaires.

1.3. PSA

Pre-treatment PSA should be recorded for all patients.

1.4. Transrectal ultrasound

This should be performed on all patients to more accurately assess the local extent of disease and measure prostate volume. It can also be used to assess the probability of pubic arch interference.

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1.5. Prostate biopsy

All patients should have biopsy proven adenocarcinoma. It is usual to take six to 12 biopsy cores with ultrasound guidance. The number of positive biopsies should be recorded to estimate tumour volume.

1.6. Bone scan

If the PSA is less than ten the probability of bone metastases is so small that scanning is unnecessary [37].

1.7. CT scan

A CT scan is of little value in assessing the local extent of prostate tumours but can be helpful in staging the pelvic lymph nodes. The same applies to whole body magnetic resonance imaging (MRI).

1.8. Pelvic phased array or endorectal MRI

This is the most sensitive imaging investigation to assess local extent of prostate cancer. It is of uncertain benefit in good prognosis patients where the probability of extra-capsular disease is low but can be helpful to evaluate patients with adverse prognostic features, particularly if they are being considered for brachytherapy alone [11,31].

1.9. Lymph node staging

For patients with poor prognostic categories the risk of lymph node involvement can be up to 30% and this is not always detected by imaging investigations. If these patients are to be taken on for brachytherapy there may be an indication to stage the lymph nodes preferably by laparoscopic node sampling before going ahead. There is, however, little information to confirm benefit.

1.10. Urodynamic studies

A clinical history should evaluate lower urinary tract symptoms and the patient should complete an IPSS symptom scoring sheet. Maximum urinary flow rate (Q_{max}) voided volume and post voidal residual urine should be measured in patients with significant symptoms.

2. Significance of the main prognostic factors

2.1. PSA

The pre-treatment PSA is one of the most significant prognostic factors. It not only has a good correlation with outcome but also is a strong predictor for the presence of extra-capsular disease [20,38,39,45,46,49]. Patients with a PSA of less than ten do well with brachytherapy alone. Those with a PSA of greater than 20 have a high probability of biochemical failure within the first 2 years but 30–50% may nevertheless remain biochemically controlled [8,12,51,

57]. Patients with a PSA of greater than 50 have such a high probability of disease outside the prostate that they are unlikely to benefit from radical local treatment.

2.2. Gleason score

Patients with a Gleason score of 6 or less do well with brachytherapy alone [8,12,51,57]. Gleason score 7 tumours have an approximately 50% probability of biochemical relapse within 5 years. Patients with a Gleason scores 6 and 7 should be distinguished according to the predominant grade (3 or 4) since a predominant grade 4 indicates a worse prognosis [44]. Those with Gleason score 8–10 tumours do badly and should be considered for other adjuvant treatment.

2.3. Stage

Patients with low volume localized disease with a small risk of extra-capsular spread do well with brachytherapy alone, i.e. stages T1C–T2B [8,12,51,57]. Some extra information on the risk of extra-capsular spread can be gained by evaluating the number of biopsies involved and the proportion of each core which contains malignancy and the presence or absence of perineural spread [2,15,40].

If brachytherapy is to be used as the sole treatment T3 cases should be excluded. For minimal T3 disease patients should be considered for external beam radiation with brachytherapy used as a boost using techniques which cover the extent of known extra-capsular spread [17].

The Partin tables use the above prognostic factors to predict the probability of extra-prostatic disease including seminal vesicle and lymph node involvement. These tables have been derived from a very large number of radical prostatectomy patients and can be helpful in identifying the risk of extra-capsular disease and selecting patients for treatment [39]. It should, however, be remembered that although many patients may have disease outside the prostate capsule it is within 2 or 3 mm of the capsule in a very high proportion and still within the volume encompassed by brachytherapy [19].

2.4. Urinary outflow

2.4.1. IPSS

The patient symptom score before treatment is the most sensitive predictor of urinary morbidity after brachytherapy. Those with a score of 0 to 8 do well with a low risk of acute retention and prolonged urethritis. Those with an IPSS score of more than 20 on the other hand have a 30–40% risk of acute retention and prolonged urethritis [25,55].

2.4.2. Prostate volume

Those with a prostate volume of 35 cm³ or less have a relatively low incidence of acute retention and urinary morbidity. This is higher for those with larger volumes [25]. Those patients with a volume of greater than 50–60 cm³ should have hormonal cytreduction if they are to be considered as candidates for brachytherapy.

This does not always reduce the risk of side effects but it is necessary to achieve a satisfactory implant.

Conventional estimation of prostate volume from ultrasound frequently under estimates the gland volume and it is important for planning purposes for it to be done with detailed planimetry using the 5 mm step section method, which is the most accurate way of measuring the volume.

While it is not possible to be categorical about patient selection, there is sufficient evidence to identify a group of patients who have been shown to do well and in whom treatment is recommended and others with less good prognostic features where results are less good and treatment might be considered investigational. There is also a group with a poor prognosis where other treatments or additional adjuvant therapy may be indicated. The selection criteria are summarized in Table 1.

3. Contra-indications to permanent seed implants

1. Life expectancy less than 5 years.
2. The presence of metastatic disease.
3. Recent transurethral resection of prostate (TURP) with persisting large prostatic defect. It is often difficult to achieve a satisfactory seed distribution and these patients have a high risk of incontinence after brachytherapy. If TURP was performed several years ago and the prostate has largely regrown patients can be considered for brachytherapy but steps should be taken to optimize the dose distribution in order to reduce urethral dose and patients should still be counselled that the risk of incontinence is higher than for non-TURP patients [1,22,27].
4. There should be no bleeding disorder and patients on regular aspirin or anticoagulants should stop it at least seven days before implantation.
5. Patients with a prostate gland of greater than 50 cm³ have a high probability of pubic arch interference, this means that part of the prostate is situated behind the bone and does not allow a geometrically satisfactory implant to be performed. These patients also need a large number of seeds and are at increased risk of morbidity. If otherwise suitable these patients can be treated after several months of hormone therapy. This usually produces a 30% reduction in volume which will often bring the gland down to 50 cm³ or less [6].

4. Other potential indications and investigational treatments

4.1. Brachytherapy as a boost after external beam radiation

It is recognized that a seed implant alone is sufficient for good prognosis patients (Gleason score 6 or less, PSA ten or less). For patients with higher Gleason scores and higher PSAs the risk of disease outside the prostate capsule

increases and some have used this as an indication to treat with external beam radiation first followed by seed implant given as a boost [6,33]. There is as yet no evidence to confirm that combining external beam radiation and brachytherapy for these patients improves their outcome.

4.2. Brachytherapy for salvage after failure of external beam radiation

It has become clear over the last few years that hitherto considered conventional doses of external beam radiation (64–68 Gy) are insufficient to achieve biochemical control in a high proportion of patients and many irradiated patients are presenting with PSA failures where disease remains localized within the prostate and could be suitable for salvage brachytherapy. The risks of retreatment are considerably higher than for brachytherapy alone and the treatment is probably therefore best reserved for those with a good prognosis who are likely to benefit [26]. For patients who initially presented with good prognosis disease and have relapsed several years after conventional doses of radiation, brachytherapy may be considered as salvage treatment provided that staging investigations confirm that their disease is localized and that prognosis remains good with PSA less than ten. For such salvage implants an optimized seed loading pattern may be helpful in order to reduce the dose to the urethra, which has already been irradiated [14].

4.3. Adjuvant hormone therapy

There is good evidence that adjuvant hormone therapy significantly improves both biochemical disease free and clinical progression free survival in advanced prostate cancers treated by external beam radiation [9] and it is likely that similar benefits might be achieved for patients who receive brachytherapy. The optimum duration of hormone therapy is unknown but it is clear that the longer hormone therapy is given the less likely it is for potency to be regained once it has stopped. For patients with Gleason scores of 7 or more and a PSA of ten or more 3 months of neo-adjuvant hormone therapy is frequently used but there is no clinical trial evidence yet to confirm that it improves outcome. There is a price to be paid in terms of side effects and decreased quality of life for patients who receive

Table 1
Indication for prostate brachytherapy

	Recommended Do well	Optional Fair	Investigational Do poorly
PSA (ng/ml)	<10	10–20	>20
Gleason score	5–6	7	8–10
Stage	T1c–T2a	T2b–T2c	T3
IPSS	0–8	9–19	>20
Prostate volume (g)	<40	40–60	>60
Q _{max} ml/s	>15	15–10	<10
Residual volume cm ³			>200
TURP ±			+

hormone therapy and there is no indication for it in patients with early disease. There is however a role for hormone therapy in reducing prostate volume as indicated above.

4.4. Equipment for brachytherapy

The key to achieving high quality implants is image guided source placement. This is best achieved with interactive transrectal ultrasound. The minimum requirements are:

1. Transrectal ultrasound with template software.
2. A stepping unit.
3. Seed planning software.

Although not essential, it can be helpful to have an image intensifier in the operating theatre and cystoscopy equipment.

In addition to the above equipment there will be a need for disposables such as stabilization and implant needles.

4.5. Facilities

Brachytherapy has to be performed in a centre which is licensed to handle radioactive material. A physicist must be available and there should be guidelines on the use of radiation regulated by the appropriate national body. The room in which the radioactive material is handled has to be specially designated for the purpose. There should be access to anaesthesia and sterilization facilities.

4.6. The clinical team

There are a number of skills and competencies required to achieve satisfactory brachytherapy and this usually requires several people. The skills required are:

1. Expertise in prostate ultrasound for planning and treatment.
2. Brachytherapy dosimetry and treatment planning.
3. Implantation skills and knowledge and experience in delivery of radiation. (In most countries supervision and delivery of radiation requires a core of knowledge and accreditation. This effectively means that the delivery of radiation requires supervision by a radiation oncologist).

The key members of a multi-disciplinary team for prostate brachytherapy should therefore include:

1. urologist;
2. radiation oncologist;
3. physicist;
4. urologist, radiologist or radiation oncologist with ultrasound skills.

Non-medical staff such as nurses and technicians are also important to the team and need to become involved in planning the service.

It is recommended that the team should participate in an

established training course and attend at least one implantation procedure before starting their own programme. It is also helpful to have an experienced prostate brachytherapist present during the first one or two procedures. It is important to measure implant quality with post implant dosimetry from the outset so that the team can learn quickly from experience how to achieve consistent implant quality.

5. Implant procedure

5.1. Pre-planning

In order to assess the amount and distribution of radioactivity it is essential to have an accurate measurement of prostate volume. The volume estimation can be combined with pre-planning. The patient is placed in the lithotomy position identical to that be used for the subsequent implant procedure and 5 mm ultrasound sections taken of the prostate from base to apex using the stepping unit. The urethra should be positioned in the middle vertical row of the template and the posterior border at the rectal interface should lie as flat as possible along the first horizontal row of the template. The coordinates of the template appear on each section and this can be used to plan the exact number and position of sources required to cover the target volume which is identified on each slice.

The planning ultrasound can be performed as an out patient procedure without anaesthetic but some centres have found that a short anaesthetic is more acceptable to patients and facilitates reproduction of the position of the planning ultrasound with the patient position for treatment.

If the volume is known accurately it is possible to combine the pre-plan with the implant during the same procedure [50,52,53].

5.2. Implantation procedure

The implant may be performed under general or spinal anaesthesia. The patient is placed in the lithotomy position with transrectal ultrasound and template in position.

Contrast medium can be inserted into the bladder to assist visualization on fluoroscopy and air-filled gel placed in the catheter to visualize the prostatic urethra on ultrasound. If a pre-plan was performed the position for implantation should correspond to the pre-plan.

The implant co-ordinates are defined from the template and the depth of insertion by a combination of ultrasound fluoroscopy and measurement.

Sources within the implant needles are inserted percutaneously under direct ultrasound control according to the pre-plan or with interactive dosimetry in a single step procedure.

Because the prostate is very mobile it is helpful to stabilize prostate movement by two or three stabilizing needles which are positioned before the sources are inserted [16,21,53].

On completion of the implant cystoscopy may be performed to remove misplaced seeds in the urethra or blad-

der. This may not be necessary because these seeds are often voided spontaneously.

5.3. Choice of isotope

Implants can be delivered either with iodine 125 which has a half-life of 60 days or paladium 103 which has a half-life of 17 days. It has been the practice in many centres to use paladium for higher Gleason score tumours which are thought to be proliferating more rapidly [42]. There is, however, little data on the proliferation rate of human prostate cancer to confirm this [29] nor any randomized trial data to show that one isotope is any better than the other.

5.4. Brachytherapy dose

Where brachytherapy with iodine 125 seeds is the only treatment, the most commonly prescribed dose is 145 Gy which is the minimum peripheral dose to the margin of the target volume specified according to the new TG43 guidelines [36]. This is equivalent to 160 Gy which was established as a result of the experience from the Memorial Hospital and was also the standard dose elsewhere for many years [7,23,43,59].

If brachytherapy is used as a boost after external beam radiation which delivers 50 Gy, the brachytherapy dose is reduced to 95 and 100 Gy [28,32,34,42].

For patients treated with paladium a dose adjustment is necessary to account for the higher dose rate. It is usual to deliver 115 Gy if treated with brachytherapy alone and with 90 Gy if delivered after 50 Gy external beam radiation [3,28,34,35]. As for ¹²⁵I new guidelines for dose specification for ¹⁰³Pd have revised these doses to 125 and 100 Gy [46].

5.5. Management of side effects

All patients develop urethritis of variable intensity and duration. Symptoms are often helped by alphablockers and non-steroidal anti-inflammatory drugs. Proctitis may also occur in a few patients and can be helped by steroid enemas. The risk of infection is low but many centres routinely use antibiotics after implantation [42].

Approximately 15% of patients may develop acute retention either immediately or in the few days following implantation [10]. This is usually due to post implant oedema and should initially be managed by urethral catheterization. In the majority of patients micturition resumes within 2 weeks as the oedema resolves. In a few patients return of normal micturition is delayed and suprapubic catheterization can be more convenient for the patient. Some may also be taught intermittent clean self-catheterization.

Transurethral resection of the prostate should be avoided if possible, at least within the first year after implantation and if then essential a transurethral incision of the prostate rather than resection may be adequate to improve outflow without risking incontinence [30].

5.6. Patient information

Very few patients or their treating doctors will be familiar with prostate brachytherapy and it is recommended that written information is provided which describes the pre-treatment investigations, the implant and the side effects and treatments which may be expected afterwards.

5.7. Follow up

Patients should be seen 4–6 weeks after implantation to check that the acute reaction is settling. They should then be seen 3 monthly for the first year and 6 monthly to 5 years and then annually. Follow up should include history and digital rectal examination, PSA test and record of urinary and bowel side effects using a validated scoring system. The effects of treatment on potency should also be recorded.

5.8. Post implant dosimetry

It is not usually possible to take away or add seeds once an implant has been completed though the addition of external beam radiation can be considered for some patients. Post implant dosimetry, however, is a valuable learning tool and there is now good evidence that the probability of achieving biochemical control is related to the quality of the implant [52]. This can only be evaluated by detailed post implant dosimetry. This usually requires a post implant CT scan from which the position of the seeds in the prostate capsule plus critical tissues can be outlined so that a full reconstruction of dose and volume can be made [4,5,18,47,48,56]. It is usual to perform the CT scan 4–6 weeks after implantation when oedema has settled [41,58].

There are a number of potential indices of implant quality but as yet insufficient long term follow up data to confirm the value of all those proposed. It is recommended that the following indices are recorded for all patients:

1. The volume implanted.
2. The number of seeds.
3. The number of needles used.
4. The total activity implanted.
5. The prescribed dose.
6. The D90, that is the dose that covers 90% of the prostate volume as defined from post implant imaging.
7. The V100, that is the percentage of the prostate volume that has received the prescribed dose.
8. V150, the volume that has received 50% more than the prescribed dose.

There is insufficient information to recommend dose or volume indices which describe the dose received by either urethra or rectum. It is important that further data is collected to see whether it is possible to identify indices which are correlated to the probability of the patient developing urinary or bowel morbidity.

5.9. Management of relapse after brachytherapy

Three successive rises of PSA with at least 3 months between each constitute a biochemical failure but do not indicate the site of failure nor is this a necessary indication for treatment. A small proportion of patients may develop a benign rise in PSA a year or more after treatment which then falls spontaneously [13].

It may be 5 years or more before clinical symptoms or signs develop and in those patients with a PSA doubling time of more than 2 years it is even longer. It may therefore be reasonable to monitor PSA to evaluate the doubling time and only treat if the doubling time is less than 1 year once the PSA is greater than ten and for other patients to perform an annual bone scan while maintaining them on surveillance. The mainstay of treatment for relapsed patients is hormone therapy.

Other salvage treatments which might be considered include radical prostatectomy, a second seed implant or external beam radiation. All are associated with a high risk of morbidity [24,54]

5.10. Radiation protection

The low energy of both iodine 125 and paladium 103 seeds is such that the dose rate at the skin surface is extremely small. Patients may therefore sleep in the same bed as their partner and be in the same room as children but it is advised that children should not sit on the patient's knee for any length of time for the first 2 months after implantation.

It is theoretically possible for a seed to be expelled in the semen on ejaculation. In the very rare event that this happens it is usually in the first one or two ejaculations. Some centres advise the use of a condom for the first two to three occasions of intercourse following implantation. Patients should be warned that prostate brachytherapy does not guarantee infertility and that pregnancy remains possible.

6. Conclusion

Many authors have demonstrated that it is possible to achieve a consistent high quality of implantation and good long term results in selected patients with localized prostate cancer.

There is general consensus about which groups of patients can be expected to do well with brachytherapy alone and which do poorly. There is an intermediate group where it remains unclear whether there is an advantage from adjuvant therapy or whether they may do better with alternative treatment. On the whole, however, patients with poor prognostic factors do poorly however treated. These questions can only be resolved by clinical trials but it seems unlikely that these will either be done or at least available within the next 8–10 years. In the meantime patients should be carefully selected and counselled on the basis of experience from non randomized studies.

The imaging and software technology which supports

prostate brachytherapy is developing very rapidly and this may well change both techniques and indications for treatment. Considerable expertise and team work is necessary to achieve an optimum result as well as keeping up to date with new advances.

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