Prostate cancer is a complex disease, with many controversial aspects of management in almost all stages of disease. The natural history of this tumor is variable and is influenced by multiple prognostic factors. Radical prostatectomy and radiotherapy are standard treatment options for disease limited to the prostate. The data in literature does not provide clear-cut evidence for the superiority of any treatment. Neoadjuvant or adjuvant hormonal therapy improves local control and survival in locally advanced disease.

The patients treated with radiotherapy would have a relatively long life expectancy, not great risk factors for radiation toxicity and a preference for radiotherapy. The advantages of radiotherapy are that it has a significant potential for cure, it is well tolerated in the majority of men especially when the modern techniques of conformal radiotherapy and intensity modulated therapy are used and it is non-invasive therapeutic options with no anesthesia risk. Expected complications like radiation cystitis, impotence and proctitis are registered in about 1% of patients.

Key words: prostate cancer, radiotherapy, localized disease

**INTRODUCTION**

Controversy has surrounded the management of patients with all stages of prostate cancer. Treatment plan is defined according to initial PSA, stage and grade of the disease and to the age and general conditions of the patient. Watchful waiting, surgery and radiotherapy (with or without hormone-therapy) could be adequate option for patients with localized disease, while hormone-therapy plus radiotherapy should be considered treatment of choice for locally advanced or bulky disease.

For high risk patients, chemotherapy has become an exciting new field of investigation. For metastatic disease, hormonal therapy is usually the treatment of choice, although there is controversy surrounding what is the optimal therapy and timing. Interest has focused upon methods of adapting endocrine therapy to offer patients optimal quality of life without compromising survival.

External Beam Radiotherapy has been widely used for the management of localized prostate cancer. New technologies in radiotherapy as conformal radiotherapy (CFRT) and intensity modulated radiotherapy (IMRT) permit the safe introduction of high dose treatments and many trials have given an improved significant role of hormonal therapy. Studies have given good evidence that androgen suppression improves outcome when added to radiotherapy, but there are still many controversies about the dose, fractionation and radiotherapy treatment volumes.

Patients selected for radiotherapy tend to be older and have higher-grade, higher stage tumors and higher PSA levels. Younger, healthier men with smaller, localized tumors have to undergo surgery.

**DIAGNOSTIC WORK-UP**

Localized prostate cancer can be divided into three prognostic groups. There are two commonly used systems. The Memorial Sloan Kettering group define low risk as T1 or T2 disease, Gleason score of 6 or less and an initial PSA of $\leq 10$ ng/ml. Intermediate risk patients have one of the prognostic indicators with a higher value and unfavorable prognosis is given for men with two or more indicators with higher values. D’Amico has defined low risk at Stage T1c/T2a and PSA level $<10$ nag/ml and Gleason score 6; intermediate risk as T2b or Gleason 7 or PSA level 10 - $<20$ nag/ml; high risk as T2c or PSA $>20$ nag/ml or Gleason score 8. Locally advanced disease may include some patients in the intermediate and unfavorable groups as well as patients with T3 or greater disease or evidence of pelvic lymph node involvement.
Before the treatment all patients should have clinical examination, digital rectal examination, histopathology assessment using the Gleason scoring system and serum Prostate Specific Antigen (PSA) level, hematological and biochemical parameters, chest X ray, radionuclide bone scan. The purpose of additional imaging is to more precisely define likely patterns of disease spread in an individual patient so as to customize treatment. CT scan and MRI present a moderate sensitivity that varies between 0 and 70% which can detect enlarged lymph nodes (upper limit of normal 10 mm) but for patients with a high risk of lymph node involvement surgical lymph node sampling presented better diagnostic procedure. CT scanning has considerably improved our ability to localize the prostate gland and has facilitated the development of more sophisticated radiotherapy treatment techniques. The information yielded by CT can be used to shape the treatment field more precisely and allow higher dose treatments to be employed. CT however does not have the inherent tissue resolution necessary to identity cancer within the gland and is not sufficiently accurate to identify early T3 disease i.e. cancer that has breached the prostate margin and/or involved the vas or seminal vesicles. CT is also poor at identifying exactly where the apex of the prostate is located. This problem with apex definition is one of the main sources of potential error in using CT scanning to define the GTV in prostate cancer.

Transrectal ultrasound equipment for prostate gland uses high (7-10 MHz) frequency transducers that provided excellent images of the prostate and its internal architecture. Color Doppler scanning may further enhance the diagnostic yield with transrectal ultrasound. TRUS however is not particularly sensitive for the evaluation of prostate cancer and the reported accuracy rates of 58%-90% have raised doubts about its reproducibility and applicability in the management of prostate cancer. Transrectal ultrasound has its main application in prostate brachytherapy where it is used for GTV (gross tumor volume) definition and to guide the treatment process itself. Transrectal ultrasound can also be used as a method for implanting radiopaque markers to aid radiotherapy planning and treatment.

Magnetic Resonance Imaging has become the most accurate method for evaluation the prostate gland. Reported staging accuracies are generally 80-90%. Either phased array pelvic coils or dedicated endorectal coils can be used. Blood products following prostate biopsy can persist for several weeks after biopsy and MRI scanning should preferably be avoided for 2-3 weeks afterwards. Prostate cancers are best-identified on T2 weighted scans. The normal peripheral gland is high signal intensity and cancers show as areas of low signal intensity on these scans. Cancers cannot reliably be demonstrated in the central zone of the glands: in this area, nodules of Benign Prostate Hyperplasia are impossible to differentiate from malignant nodules.

CONVENTIONAL RADIOTHERAPY

External beam irradiation was first used as a curative modality for localized prostate cancer in the 1950’s, when the highly penetrating mega-voltage beams from cobalt-60 teletherapy units and linear accelerators became available. Applied using the then newly developed methods of dosimetry and treatment planning, mega-voltage radiotherapy permitted the delivery of tumoricidal doses to prostate tumours without excessive damage to the skin and the normal tissues around the prostate. Experience accrued with conventional techniques indicates that external beam radiotherapy is effective in localised prostate cancer. Conventional radiotherapy techniques uniformly encompass certain portions of the bladder and rectum as safety margins included in the volume receiving the highest radiation doses. Consequently, attempts to increase the tumour dose to further improve local control are frequently restricted by the sensitivity of the bladder and the rectum to the effects of radiation.

In patients with T1-T3 prostate cancer treated with external beam therapy alone during the 1970s and 80s in the pre-PSA era has been documented good treatment results and outcome in some large studies. Local tumour control becomes increasingly poor as stage increases with reported rates of tumour local control of 83% for T1, 65-68% for T2 but failing to 44-75% for T3 disease. Perez and al reported results in 963 patients with carcinoma of the prostate who were monitored for a minimum of 3 years after radiation therapy. The 10-year actuarial disease-free survival rates were 70% for stage A2 (T1c), 60% for B (T2), 45% for stage C (T3), and no survivors for stage D1 (T4). The overall survival rate was about 10% higher.

Hanks and all in 1348 patients with stage B and C tumors, reported an actuarial 5-year local recurrence rate of 37% for patients with stage C lesions treated to doses of less than 60 Gy, 36% for 60 to 64.9 Gy, 29% for 65 to 69.9 Gy, and 19% for 70 Gy or more. By 7 years, 32% of patients receiving 65 to 69 Gy and 24% of patients treated with higher doses had local recurrence.
The same authors described results with definitive radiation therapy (60 to 70 Gy) for 619 patients treated in the Patterns of Care study. For those with stage A disease, the 5-year survival rate was 75%; with stage B, it was 85%; and with stage C, it was 58%. At 10 years, the survival rates were 50%, 61%, and 38%, respectively.

Kuban and al. reported on 652 patients with clinical stage A2 to C prostatic carcinoma treated with external irradiation. The 10-year clinical disease-free survival rates were 66% for 82 patients with stage A2 (T1b), 57% for 79 with B1 (T2a), 48% for 73 with B2 (T2b,c), and 29% for 47 with C (T3 and T4) tumors. The corresponding biochemical disease-free survival rates were 35%, 18%, 21%, and 11%, respectively. The 10-year clinical survival rates correlated with pretreatment PSA were 80% in 80 patients with PSA of 4 ng/ml or less, 40% in 74 patients with 4.1 to 10 ng/ml, 23% in 70 patients with 10.1 to 20 ng/ml, and 13% in 44 patients with PSA greater than 20 ng/ml. The 10-year biochemical disease-free survival rates were 59% and 18% for the first two groups; there were no long-term survivors among the patients with PSA greater than 10.1 ng/ml.

The clinically assessed incidence of local recurrence after definitive irradiation ranges from 0% to 20% for stage T1b, 5% to 30% for T2, and 12% to 40% for T3 tumors. However, when the data are analyzed using actuarial methods, the incidence of clinically detected local recurrence is higher: at 10 years, it is 20% for stage T1b, 24% for T2, and 40% for T3 lesions.

Zagars and al. in a review of 648 patients with localized carcinoma of the prostate treated in the pre-PSA era (1966 to 1988), reported 10-year local recurrence rates of 12% in patients with T1, 25% with T2 and T3, and 32% with T4 tumors, as assessed by clinical examination. The inci-
dence of distant metastasis was 10% for T1, 25% for T2, 40% for T3, and 60% for T4 lesions. There was a close correlation between Gleason score and incidence of distant metastasis: 15% for Gleason scores of 2 to 4, 35% for scores of 5 to 6, 52% for score of 7, and 65% for scores of 8 to 10. The local recurrence rate ranged from 15% to 25% for patients with Gleason scores 2 to 6 and was about 38% for patients with Gleason scores of 8 to 10. In 707 patients treated in the PSA era (1987 to 1993), there was a close correlation between the pretreatment PSA levels and 5-year actuarial biochemical relapse rate (about 10% for < 4 ng/ml, 40% to 45% for 10 to 20 ng/ml, and 80% for higher PSA levels).9

In a study of 120 patients Hank’s and al. presented biochemical control of only 28% in T3 disease compared to 54% and 72% in T2 and T1 disease in a mean follow up time of 12.6 years. High Gleason score correlated with poor outcome with PSA control rates of only 18% for Gleason score 7 and 0% of men with Gleason sum 8 or 9 cancers. More contemporary series using a mean dose of 69 Gy showed 5 year PSA control rates of 81%, 68%, 51% and 31% for men with initial presenting PSA levels of < 10, 10-20, 20-<30 and ≥ 30 ng/ml respectively. It is clear from these results that for men with bulky local disease, high grade cancers of PSA levels > 20 ng/ml that conventional dose radiotherapy alone gives poor long term disease control and strategies to improve outcome are required.10

The clinical prospective, non-randomized study on 170 patients with prostate adenocarcinoma treated by definitive radiotherapy was conducted at the Institute for Oncology and Radiology of Serbia. The aim was to evaluate the role of radical radiotherapy in localised prostate cancer concerning local control, disease free survival (DFS), overall survival (OS) and treatment morbidity, as well as the impact of initial PSA value on treatment results.11

Patients characteristics are shown on table 1.

External beam radiotherapy was delivered with megavoltage linear accelerator (10, 18 MeV). Local or locoregional technique included anterior and posterior parallel opposed fields with tumor dose of 45- 50 Gy in 22- 24 fractions/ 2, 08 Gy per fraction, followed by a boost to the prostate of 15- 20 Gy in 8 – 10 fractions with two lateral parallel fields (four field technique) bringing the total tumor dose within the prostatic volume to 65 Gy in 30-32 fractions (Figure 1, 2).

| TABLE 4 | RESULTS |
|---|---|---|
| Arm1 RT+GnRH analog 2m neoadj+2 m conc | Arm2 only RT | p |
| prostatic volume (ml) | 21.7 | 48.5 | 0.003 |
| PSA(ng/ml) | 3.5 | 48.1 | 0.005 |
| 2y DFS | 90% | 72% | 0.001 |
| 2y OS | 100% | 95% | 0.07 |

![FIGURE 1 ANTEROPOSTERIOR SIMULATOR FILM (LOCOREGIONAL TECHNIQUE)](image1)

![FIGURE 2 ISODOSE DISTRIBUTION FOUR FIELD TECHNIQUE (50 Gy AP/PA+15 Gy BY LATERAL FIELDS)](image2)
Fifty-four patients (31.8%) relapsed. The most frequent site of relapse were bones (15.3%). Biochemical relapse only was registered in 14/54 patients (8.2%). Mean time to progression was 19.5 months (range 6-42). DFS and OS at 5 and 10 years were 60.44% vs 66.47% and 53.31% vs 47.18% respectively. Disease specific survival was 75.61% and 60.67%. Patients with initial PSA value <10 ng/ml had statistically superior disease free survival comparing with patients with PSA 10 ng/ml (81.88% vs 53.79%) (p=0.020), but in overall survival this was not registered (70.46% vs 58.89%) (p=0.946) (Figure 3, 4). Overall survival rates shows no significant difference according to PSA level (p=0.95) (Figure 3 and 4).

Disease-free survival shows significant difference according to PSA level (p=0.02).

Statistical analysis of PSA nadir as prognostic factor = 4 ng/ml and up to 4 ng/ml showed statistical significant difference in OS (82% vs. 60%) (p=0.03) and DFS (75% vs. 40%) (p=0.0003) (Figure 5, 6).

Overall survival rates shows significant difference according to PSA level after RT (p=0.03) (Figure 5 and 6).

Disease-free survival shows high significant difference according to PSA level after RT (p=0.0003).

Acute complications were registered (mild and moderate) in 113 patients (66.47%) and late sequelae (grade I and II) in 37 patients (21.76%).

Radical radiotherapy for localised prostate cancer is effective treatment option in some patients with good local control, long term cure; present treatment tolerance providing good quality of life and PSA initial level is a strong prognostic factor, in treatment outcome.

CURRENT RADIOTHERAPY TECHNIQUE

In recent years, radiotherapy has witnessed major technological advances with the advent of 3D-conformal radiotherapy (3D-CRT). Conventional irradiation with the classic four-field technique, in fact, could safely be carried out to a total target dose of 65-70 Gy. The frequent persistence of local residual tumour following conventional radiotherapy at these dose levels has been a matter of concern in the literature. This was likely due to failure to eradicate the disease from intrinsically resistant prostate tumour clonogens, and from uncertainties in tumour delineation, organ motion, and patient positioning form day to day. 3D-CRT has, therefore, been developed with the aim of addressing some of these issues. 3D-treatment planning is based on the ability to define anatomically each pixel. 3D CRT is a high precision technique which
improves local control by means of dose escalation, without increasing the risk of morbidity.

The patients treated with conformal and intensity modulated therapy receiving higher doses more recently than those receiving conventional doses. These doses are higher than most commonly accepted limits of 70 Gy, which are achieved with conventional techniques of radiation, planning and application of the same. The standard dose has been 70 Gy in 35-38 fractions to the prostate seminal vesicles, which appears to be appropriate for patients with low risk cancers. In practice, for localized stages with good prognostic indicators (PSA 10 ng/ml and Gleason score 7) conformal radiotherapy given up to 70-72 Gy is still recommended as it offers the same results as those with dose escalation. For patients with intermediate or high-risk patients, doses between 75-80 Gy are better. Several clinical studies have emphasized the improvement of biochemical response and control with use of highly conformal doses - the escalation of the same.

Confirmation that dose escalation does improve biochemical control rates comes from the results of the MD Anderson randomized trial conducted between 1993 and 1998. Over 300 men with localized prostate cancer (T1-T3) received radical radiotherapy to the prostate and seminal vesicles and were randomized to either conventional dose (70 Gy) or high dose (78 Gy) treatment. With a median follow up of 60 months, the biochemical control rates for the 70 and 78 Gy arms at 6 years were 64% and 70% respectively (p=0.03). The benefit of dose escalation was greater for those with pretreatment PSA 10 ng/ml and biochemical control rate was 43% for those who received 70 Gy versus 62% for the 78 Gy arm (p=0.01).

In the treatment of localized prostate cancer, by means of significant exclusion of adjacent normal tissues from the high dose region, 3D-CRT has been shown to reduce the risk of rectal and bladder toxicities, thus enabling safe dose escalation to unprecedented dose levels (80-86 Gy). Recently, further technological advancements have been conducted into the clinical implementation of intensity modulated radiotherapy (IMRT). This technique carries the potential of even greater normal tissue sparing in selected cases where the anatomical relationships of the prostate and seminal vesicles relative to the adjacent critical structures do not allow dose escalation with conventional 3D-CRT.

**BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY**

Patients with low risk, early stage disease with favourable prognostic factors (PSA 10, GPS = 6) may be effectively treated with permanent seed implants (iodine 125 or palladium 103 seeds), where long term results are similar to those of prostatectomy or external beam radiotherapy. Candidates for brachytherapy as a sole treatment modality should also be devoid of urinary symptoms to avoid the risk of urinary retention. Patients with large prostate (60 gr) or symptoms of bladder outlet obstruction (IPSS score 15), or a previous transurethral resection of the prostate are not ideal candidates because of increased risk of urinary morbidity. The recommended prescribed doses for monotherapy are 145 Gy for 125-Iodine and 125 Gy for 103-Palladium.

Patients with intermediate prognostic factors and the presence of risk of extracapsular extension, can be treated with combination of brachytherapy and external-beam radiotherapy, as an alternative to exclusive high dose 3D-CRT with conflicting results. An alternative strategy is to combine brachytherapy with external beam radiotherapy to produce a high dose conformal boost. Brachytherapy may be given using either low dose rate permanent seed implants with Iodine-125 or Palladium-103 or high dose rate temporary implants with Iridium-192. The fall off in dose from the implanted sources is rapid following an inverse square law so that treatment of extra capsular disease is unreliable. The corresponding boost dose after 40-50 Gy external beam radiotherapy are 110 Gy for 125-Iodine and 100 Gy for 103-Palladium. Post-implant dosimetry should be always performed.

359 high risk patients were treated in multicenter study with external beam radiotherapy (46-50 Gy) and high dose rate (HDR) boost of with three different brachytherapy boost regimens: 15 Gy x 2, 3-4 Gy x 3 or 5.5 Gy x 4/11 Gy x 2 depending of institution. Results were similar from the different institutions with a PSA control rate of 69% at 5 years and 95% cause specific survival. In the study of Martinez et al. 207 men were treated in dose escalation trials using 5.5 Gy x 3 to 11.5 Gy x 3 interdigitated with external beam radiotherapy to a dose of 46 Gy. For intermediate and high risk patients, 5 year PSA control was 74% overall and 50% for the highest risk group. Results appeared to improve with higher doses. Grade 3 or more genito-urinary and rectal side effects were reported in 8% and 1% of men respectively.

Astrom et al report a 61% 5 year PSA control rate for intermediate/high risk patients using 50 Gy external beam radiotherapy and HDR of 10 Gy x 2F. Moderate genito-urinary complications were seen in 36% of men and gastro-intestinal side effects in 17%. There have been no randomized comparisons between these combined modality treatments and high dose external beam radiotherapy alone - both are satisfactory ways of delivering high dose treatment and the choice is principally dependent on local facilities, skills and interest.

**PSA LEVEL AFTER RADIOTHERAPY**

There is still controversy concerning what should be a normal PSA after radiotherapy, and at what moment the PSA-nadir should be achieved. After radiotherapy the prostate gland has not been totally destroyed and measurable serum PSA is to be expected. Classically post-therapeutic reduction of serum PSA levels 4 ng/ml have been considered evidence for successful treatment since this value represents the upper limit of the normal range in the general population. The "normal" postirradiation PSA level may be determined as that value associated with long term disease free survival.

The median time to obtain a nadir following radiation therapy varies between 12 and 28 months. The PSA nadir value following radiotherapy represents a strong pre-
dictor of outcome. In Canadian study the median nadir PSA in patients without signs of disease was 0.5 ng/ml after 2 years from radiotherapy at 5 year follow up. For those with local failure it was 1.6 ng/ml at 16 months, and for all failures 1.8 ng/ml at 13 months 19.

**RADICAL PROSTATECTOMY PLUS RADIOTHERAPY**

While diagnosed, 10-15% of patients with clinically documented prostate carcinoma have a penetration through the prostate capsule (AJCC T3-T4), with no registered regional lymph nodes or distant metastasis.

External beam radiotherapy has been, for a long period, the therapy of choice in treatment of locally advanced prostate carcinoma, since a surgical resection would result in pathohystological positive margins and, therefore, an adjuvant postoperative radiotherapy would be necessary in order to achieve local control and potentially effective curing. Radical prostatectomy is widely used in treatment of prostate cancer. PSA following it should be undetectable. Postoperative PSA values indicate carcinoma relapse. Radical surgery and external beam radiotherapy offer the same 10- years survival results in patients with localized stages c T1a-b, c T1c, c T2a-b, N0, M0.

The percents of local relapse within a postoperative period of 10 to 15 years ranges from 20-60%, depending on the method of detecting and reporting 22. The management of margin positive disease is still controversial.

Current options include expectant management (surveillance), radiation therapy and hormonal treatment. In a large Dutch series of radical prostatectomy with 63% pT3 tumours followed by surveillance only, local recurrence rate was 14 and 39% at 5- and 10-years and the clinical progression rates were 34 and 75%, respectively, many more patients experiencing distant progression than local recurrence 20. Radiation therapy may be beneficial after radical prostatectomy in some patients with pT3 prostate cancer: in one study with a median follow-up of 3–5 years post-operative irradiation seems to increase the percentage of patients who are free from PSA relapse. However no long-term data showing a survival advantage to postoperative radiation therapy are available today 26.

Within 1778 patients operated through radical prostatectomy, Catalona et al. have recorded positive margins in 21%, 9% had seminal vesicle infiltration and only 2% were with positive nodes 21. Pound et al. have proved within 1623 operated patients that positive surgical margins are significant only in high grade tumours 21.

The main question, nowadays, is: what is the best therapy for patients after radical prostatectomy and with positive margins?

The issue is, furthermore, complicated by additional factors:
- whether the margins are really positive, and if so
- what is the best therapy.

Nowadays, there is no consensus on the above asked question 22.

1. pathologists are on their way to agree upon parameters (volume, grade, margins) as well as on methods of their measuring and documenting;

2. a 5-year postoperative PSA level is a very good substitute endpoint for a persistent disease after a radical prostatectomy: after 5 years, the hazard for patients with undetectable PSA is almost 0 (none): seminal vesicle involvement has a 75% chance of being a persistent disease, but the involvement range is still a significant, yet fairly defined factor; pelvic lymph nodes involvement is almost a certain sign of a persistent (usually systemic) disease; positive margins are a significant factor, but 50% of patients with positive margins are likely to be cured. It particularly concerns those with positive margins primarily in prostate apex; significance of tumour volume as an independent prognostic factor in a persistent disease is still controversial; while positive margins and tumour margins are controversial areas, it is believed that postoperative risk must be individual and carefully discussed with the pathologist 22.

Radiation therapy of the prostate bed is used for treatment of the patients with increased PSA or a proved local recurrence. There is no prospective randomized study that would document the efficacy of this therapy, thus small-range studies are not conclusive enough. There is a need for better identification of the patients that are to benefit from a radiotherapy, as well as for definition of the best way to apply the same.

**RADIOTHERAPY PLUS HORMONOTHERAPY**

Hormonal therapy can combined with radiotherapy on different ways: as neoadjuvant, adjuvant, concomitant and adjuvant hormonotherapy, neoadjuvant and adjuvant, and neoadjuvant, concomitant and adjuvant hormonotherapy. Neoadjuvant and adjuvant hormonal therapy when started simultaneously with radiotherapy improves local control and survival. This has been confirmed in many studies. The exact length of hormonal therapy remains controversial.

EORTC trial 22863 by Bolla et al. was the first randomized study which reported an overall survival benefit for adjuvant androgen deprivation in men receiving radical radiotherapy for prostate cancer 23. Since then our understanding of the appropriate use of hormone therapy as an adjuvant to radiation has been informed by the results of several important randomized trials using short course neoadjuvant (approx 6 months) or longer courses (=2 years) of adjuvant androgen suppression.

Both in the setting of organ-confined disease and of locally advanced high-risk disease.

RTOG 86-10 randomized 470 men with locally advanced disease to radiotherapy with or without 4 months neoadjuvant total androgen suppression. With a median follow-up of 8.7 years, there was a non-significant trend towards improved overall survival for the group receiving both radiation and hormone therapy (8-year survival: 53% versus 44%, p = 0.10). A statistically significant survival advantage was seen in the subgroup of 129 men with Gleason 2-6 disease, in whom 8-year overall survival was 70% for combined treatment versus 52% for radiation alone 24.
D’Amico and all randomized 206 patients with intermediate or high risk localized disease between radiotherapy alone and radiotherapy and a 6 month course of androgen suppression starting 2 months before radiotherapy. After a median follow-up of 5 years, an overall survival advantage was seen with the addition of hormonal treatment (88% vs. 78% \( p = 0.04 \)) with an increase in 5 year survival free of salvage rate from 57% to 82% (\( p = 0.002 \)) with the addition of hormonal treatment\(^{25}\). The optimal timing of short course hormonal therapy has been addressed in RTOG study 94-13. In this study, patients with an estimated risk of lymph node involvement of \( \geq 15\% \) were randomized to 4 months androgen suppression either before and during or after radiotherapy. There was an advantage for the initial hormone treatment approach in men who additionally had pelvic irradiation. The acceptability of short term androgen suppression has been assessed in a substantial\(^{25}\).

RTOG 92-02 tested short versus long course androgen suppression, in over 1500 men with locally advanced disease (T2c-T4). All received radical radiotherapy with 4 months of neoadjuvant total androgen suppression, and were randomly allocated to an additional 2 years of adjuvant Goserelin or to observation. Overall, the duration of adjuvant hormone therapy had no effect on survival. Five-year overall survival was 78% versus 79% for long-term and short-term adjuvant therapy, respectively. However, subgroup analysis of patients with Gleason 8-10 disease demonstrated a significant survival advantage for long-term adjuvant therapy, with 5-year overall survival of 80% versus 69%\(^{27}\).

EORTC trial 22863 tested long course androgen suppression in 405 men with T3-4 and/or high grade prostate cancer. Patients received pelvis and prostate radiotherapy alone (70 Gy) or radiotherapy plus concurrent and adjuvant Goserelin for 3 years. The five year overall survival was significantly better in the combined treatment arm (79%) compared with the radiotherapy alone arm (62%) (\( p = 0.0002 \))\(^{(24)}\). In RTOG 85-31, 977 men with T3 and/or N1 disease were randomized to radiotherapy alone or the addition of long term adjuvant hormonal therapy which started at the end rather than at the beginning of radiotherapy. Initial results showed a statistically significant cause specific and overall survival advantage in favour of the combined treatment arm in the sub-group of patients with Gleason 8-10 tumours, but updated results show this effect now extends to the entire study population (53% vs. 38%, \( p = 0.004 \))\(^{28}\).

Many randomized RTOG trials using different schedules of hormone-therapy combined with radical radiotherapy. The results have shown a significant increase in local control, disease free survival and time to distant metastases in patients with bulky and not-bulky disease. In studies 85-31 and 92-02 an increased survival was shown in group of patients with high Gleason scores. Patients with low Gleason score treated with short-course neoadjuvant hormonal therapy fared better than those treated with radiotherapy only in RTOG study 86-10. Only EORTC trial 22863, has showed a statistical significance in an improvement in overall survival. This result are controversial and needs further randomized studies (table 2).

At the Institute for Oncology and Radiology of Serbia between January 1991 and December 1999, 55 patient were included in the study. They were divided in two groups: group I - 30 patients treated with external beam radiotherapy, delivered with high energy photons, to a total dose of 65 Gy combined with neoadjuvant hormonal therapy with LHRH analogue (goserelin 3,6 mg). Hormonal therapy was initiated two months prior to the beginning of radiotherapy and was administered in 4 consecutive cycles, one every four weeks. Group II had only radiotherapy.

Patients characteristics and results of the treatment are shown in tables 3 and 4. We noted statistically significant difference in decreasing of prostatic volume, PSA level and better DFS and OS in group of patients with combined neoadjuvant hormonal and radiotherapy, group I\(^{29}\).

**RADIOThERAPY COMPLICATIONS**

Late sequelae in patient treated with conventional radiotherapy occurs 3–6 months after the end the treatment. The incidence of late toxicity is lower for doses up to 64 Gy but increases with dose for treatments exceeding 70 Gy (from about 4 to 9% at 3 years). The incidence of serious urinary sequelae (haematuria, cystitis, urethral stricture and/or bladder contracture) is low (about 7%), with urethral stricture the most frequent event and a previous transurethral resection of the prostate (TUR-P) the most frequent favouring cause in the case of a too early radiation treatment. Serious intestinal sequelae (proctitis, diarrhoea, rectal bleeding or stricture) occur in less than 3.5% of cases with a significant involvement of the anterior rectal wall as the most important variable for increased toxicity. Hanks et al. reported an overall complication rate of about 5% in 1293 patients which were included in Patterns of Care study. The most frequent urinary sequelae were urethral stricture and cystitis with intermittent hematuria (3% to 6%). Bladder fistula, hemorrhagic cystitis or ureteral stricture occurred in fewer than 0.5% of patients. The incidence of severe anal and rectal injury requiring colostomy was less than 1%\(^{31}\). Perez et al. reported one rectovesical and one vesicosigmoid fistula in 738 patients (0, 27%)\(^{31}\). Introduction of 3D-conformal radiotherapy, and intensity modulated radiotherapy, made possible significant escalation in prescription dose, while keeping the dose to the critical structures to relatively safe levels. The risk of late side effects can be effectively assessed through the use of dose-volume histograms (DVH’s). Radiation-induced late toxicity, following high dose radiotherapy with modern treatment techniques, is generally acceptable, and it usually entails rectal side effects. Patients treated with 3D-RT at high dose, however, may experience rectal bleeding (up to 17% at 5 years for doses ranging from 75 to 81 Gy). The implementation of intensity modulated radiation therapy by reducing the volume of rectal wall exposed to high dose, has resulted in as significant reduction of late rectal bleeding (2% with IMRT versus 17% with 3D-RT)\(^{31}\).
SUMMARY

Karcinom prostate je kompleksna bolest, sa više kon-
traveznih aspekata u lečenju svih stadijuma bolesti. Pri-
roda ovog tumora je promenljiva i pod uticajem mnogo-
brojnih prognostičkih faktora. Radicalna prostatektomija i
radioterapija su standardne terapijske opcije za bolest koja
je ograničena na prostat. Podaci u literaturi ne daju jasne
podatke o superiornosti neke metode. Neadjuvantna ili
hormonska adjuvantna terapija poboljšavaju lokalnu kon-
trolu i preživljavanje kod lokalno uznapredovale bolesti.
Bolesnici tretirani radioterapijom imali su relativno dugo
preživljavanje, neznelike rizik faktore radiacije tokšć-
nosti i sklonost za radioterapiju. Prednosti radioterapije
su, da ona ima signifikantan potencijal da leči, dobro je
toleriše većina bolesnika, specijalno kod tehnički moderne
i konformalne terapije prilagodjenog intenziteta i može se
reći da je to neinvazivna terapijska opcija, gde anestezija
nije potrebna. Očekivane komplikacije kao postiradijacii-
oni cistitis, impotencija i proktitis, su zabeleženi u oko 1%
bolesnika.

Ključne reči: karcinom prostate, radioterapija, lokal-
zovana bolest

REFERENCES

trends in national practice for external beam radiotherapy
for clinically localized prostate cancer: 1999 Patterns of
care survey of prostate cancer. Int J Radiat Oncol Biol
2) D'Amico AV, Whittington R, Malkowicz SB. et al.
Biochemocal outcome after radical prostatectomy, exter-
nal beam radiation therapy or interstitial radiation therapy
for clinically localized prostate cancer. JAMA 1998, 280
(11),969- 974.
3) Roach M, Pickett B, F- Akayawa P. et al: Implementa-
tion of newer radiotherapeutic technology in the men-
247- 268.
4) Blasco JC, Ragde H, Schumacher D. et al: Transper-
ineal percutaneus iodine- 125 implatation for prostate car-
cinoma using transrectal ultrasound and template guid-
5) Jager GJ, Ruijter ET, van de Kaa CA et al: Local
staging of prostate cancer with endorectal MR imaging:
Correlation with histtopathology. AJR 1996, 166, 845-
852.
6) Dearmaley DP. Radiotherapy in locally advanced
prostate cancer. EJC, Supplements 2005, 3, 317
7) Perez CA. Prostate. in: Principle and practice in ra-
diation oncology 3 rd edition edd: Perez CA and Braddy
LW. Lippincot- Raven 1998, 1583- 1694.
8) Kuban DA, El-Mahdi AM, Schellhammer PF: Pro-
tate specific antigen prediction and posttreatment evalu-
at on of outcome after definitive irradiation for prostate
9) Zagars GK, Pollak A Kavady VS. et al. Prostate can-
cer and radiation therapy: The message conveyed by se-
rum prostate- specific antigen. . Int J Radiat Oncol Biol
10) Hanks GE, Hanlon AL, Hudes G. et al. Patterns of
failure analysis of patients with high pretreatment prostate
— specific antigen level treated by radiation oncology: the
need of improved systemic and locoregional treatment. J
Clinical Oncol 1996, 14, 1093-1097.
11) Radosevic- Jelic Lj., Stojanovic S. Babic D. Exter-
nal beam radiotherapy in patients with localised prostate
cancer: treatments results and patern of failure. Journal of
BUON, Proceedings/ Educational book, 5 th Congres of
12) Zlotecki AR. External beam radiotherapy in the
Management of Carcinoma of the prostate. Cancer Control
2001, 8, 503- 510.
13) Hanks GE, Hanlon AL, Schultheiss TE et al. Dose
escalation with 3D conformal treatment: five year out-
comes, treatment optimisation and future directions. Int J
14) Zelefsky MJ, Leibel SA, Gandin PB et al. Dose es-
calation with three- dimensional conformal radiation ther-
apy affect the outcome in prostate cancer. Int J Radiat On-
cancer radiation dose response: results of the M. D. An-
derson phase III randomised trial. Int J Radiat Oncol Biol
16) Galalae RM, Martinez A, Mate T. et al. Long term
outcome by risk factors using conformal high dose rate
brachytherapy boost with or without neoadjuvant andro-
gen suppression for localized prostate cancer. Int J Radiat
17) Martinez A, Gonzalez J, Spencer W. et al. Confor-
mal high dose rate brachytherapy improves biochemical
control and couse specific survival in patients with pro-
cancer and poor prognostic factors. J Urol 2003, 169,
974- 980.
18) Astrom L, Pedersen D, Mercke C. et al. Long- term
outcome of high dose rate brachytherapy in radiotherapy
of localized prostate cancer. Radiother Oncol 2005, 74,
157- 161.
for localized prostate cancer: assessment of results of


