Background: Combination of permanent interstitial brachytherapy based on radioactive iodine with external beam radiotherapy is an alternative to other treatment modalities, such as radical prostatectomy or external beam radiotherapy alone in patients with intermediate-risk localized prostate cancer. In this article we report our experience with this combination modality.

Methods: Among patients who were treated in our institute with brachytherapy, there were 64 patients who received combination therapy for the above indication. Combination therapy enables administration of 110 Gy as brachytherapy and thereafter 45 Gy as external beam radiation. All patients received adjuvant androgen deprivation therapy for 6 months. The prospective follow-up was done with the aid of validated evaluation instruments (questionnaires).

Results: Combination therapy was administered without additional urinary (IPSS-based) or sexual (IIEF-based) side effects above those with brachytherapy alone. No severe perianal and lower intestinal tract side effects were observed. Short-to-moderate-term results based on serum PSA levels are encouraging, and are not inferior to what is accepted by the literature for other radical therapies.

Conclusion: Combination of permanent interstitial brachytherapy and external beam radiotherapy in the appropriate patients does not cause any additional morbidity, and its biochemical results justify its application. This modality should be offered as an accepted and good alternative to other radical treatment options, to men with prostate cancer with moderate risk factors.

Key words: prostate cancer, brachytherapy, external radiation Introduction

INTRODUCTION

Permanent interstitial brachytherapy based on iodine-125 seeds is becoming a favorite modality for the treatment of localized prostate cancer⁴⁻⁵. Brachytherapy permits delivering of maximal radiation to the prostate three-dimensionally, and enables meticulous radiation planning in the prostate and periprostatic tissues. Based on these accurate radiation calculations, it is possible to raise radiation dose above the dose accepted for external beam radiotherapy. The renewed interest in brachytherapy in the last two decades originates from the development of transrectal ultrasonography for imaging the prostate and of real-time computerization in the operating theatre. Current studies on treatment of localized prostate cancer indicate that the results of permanent interstitial brachytherapy are not different from radical prostatectomy nor external beam radiotherapy⁴⁻⁵. Non-controlled comparison showed similar results for these three treatment modalities in patients with good prognostic factors⁶.

Accumulative experience indicates that it is possible to receive encouraging results with brachytherapy alone (monotherapy) in patients with good prognostic factors, while in patients with less than good prognostic factors, brachytherapy alone is not sufficient. Over the last years, criteria have been defined for the treatment of brachytherapy as monotherapy or as combination therapy with external beam irradiation. Combination therapy for patients with moderate prognostic factors includes internal radiation with approximately two-thirds of the total radiation dose administered in brachytherapy as monotherapy, with the addition of external radiation in a relatively wide field which includes regional lymph nodes. Another approach combines brachytherapy with external beam radiotherapy and androgen deprivation therapy for several months⁷⁻⁸. This approach is based on the encouraging results of the treatment with hormonal regimens in addition to external beam radiotherapy. Combination of two radiation modalities enables administration of large amounts of
radiation to the target organ – the prostate, with additional radiation in a wider field which includes periprostatic tissue and regional (pelvic) lymph nodes. The above combination ensures that in cases where there might be microscopic penetration of the disease outside the prostate, there will still be a chance for cure by local treatment. Those who question the combination approach raise the concern that it may result in accumulation of side effects, mostly in the genitourinary and the lower intestinal systems.

We hereby report our experience with combination of permanent interstitial brachytherapy and external beam radiotherapy with the use of androgen deprivation.

PATIENTS AND METHODS

In the seven years since we started to administer brachytherapy based on iodine-125 seeds to patients with localized prostate cancer, over 600 patients were treated at the Tel-Aviv Medical Centre. Sixty four patients (11% of the patients treated with brachytherapy) were treated with a combination of permanent interstitial brachytherapy with external beam radiotherapy and a 6-month androgen deprivation treatment. This group is the study group we report hereinafter. This is an observational cohort study, and its main aim was the prospective documentation of genitourinary side effects using validated questionnaires.

PATIENTS

Inclusion criteria for permanent interstitial brachytherapy, either as monotherapy or as combination with external beam radiotherapy, were Gleason score 7 or less, serum PSA levels less than 20 ng/ml and clinical stage up to T2b. Patients who underwent open surgery for the prostate or were less than 5 years from a transurethral resection of the prostate were not candidates for brachytherapy. Pre-operative investigation might have included bone scintigraphy and computed tomography for imaging abdominal and pelvic organs, according to the referring physician’s decision. One patient underwent pathological examination of regional lymph nodes which were laparoscopically resected.

All patients with Gleason score 7, independent of PSA levels and clinical stage, were defined as moderate risk group, and were referred to combination therapy. From all the patients who were referred for consultation as for their applicability to brachytherapy treatment, 64 men who were in the moderate risk group were treated with combination therapy and short-term androgen deprivation treatment. We hereby report with no exception all treated patients in the moderate risk group.

TREATMENT

The brachytherapy method used by us was previously reported\(^9\)\(^{11}\). Patients, who were offered combination treatment and gave their informed consent, underwent transrectal ultrasonography in order to measure the prostate and to plan the radiation, with the use of a designated program for volume measurement by Bruel and Klar (Denmark). The exact measurement was done few weeks before brachytherapy time, and at this time complete androgen blockade was started, using two 3-months GnRH-analogue injections and oral anti-androgens. Androgen deprivation therapy was therefore continued for 6 months. The radiation physicist, who is a part of the brachytherapy team, orders the iodine-125 seeds for the patients in the appropriate amount and specific activity for combination of the two radiation modalities.

At the appropriate time, in the outpatient operating theatre, under general or regional anesthesia, implantation of the seeds is carried out. The radiation was planned for each patient by a designated program (VARIAN, UK). Each patient received a minimal peripheral radiation dose of 107 Gy (instead of 160 Gy, the full accepted dose in brachytherapy alone). At the end of the procedure, fluoroscopy was done to verify the location of the implanted seeds. Patients were discharged without an indwelling urethral catheter and were invited after a month for a follow-up visit, when a computed imaging was done for verification of the seeds location, and the radiation dose delivered to the patients was re-calculated.

After a time interval of 6-8 weeks, with the results of the computed imaging-based calculations, patients were referred for completion of external beam radiotherapy in a dose of 45 Gy, with daily doses of 1.8 Gy. The external beam radiotherapy, lasting 25 sessions, was administered in a center close to the patient’s residence, and coordinated with the radiotherapist to cover a wide field including regional lymph nodes.

FOLLOW-UP

All patients were examined at 1, 3, 6, 9 and 12 months after brachytherapy, biannually from the second year and annually from the fifth year. During each visit, blood was taken for PSA level and the patients filled validated questionnaires regarding urinary disorders (International Prostate Symptom Score, IPSS) and sexual function (International Index of Erectile Function, IIEF). Patients underwent rectal examination annually and were questioned regarding consumption of drugs improving urinary symptoms and sexual function.

RESULTS

The mean age of the 64 patients in the study group was 67 years (range 54-81 years). Table 1 shows basic characteristics: clinical stage, pre-treatment PSA levels and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>64</td>
</tr>
<tr>
<td>Mean age</td>
<td>67 years (range 54-81)</td>
</tr>
<tr>
<td>Pre-treatment prostate volume</td>
<td>42.4±6.6 cm³</td>
</tr>
<tr>
<td>Pre-treatment PSA</td>
<td>8.6±3.4 ng/ml</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>T1c - 53 patients (83%)</td>
</tr>
<tr>
<td></td>
<td>T2 - 11 patients (17%)</td>
</tr>
</tbody>
</table>


\(32\) H. Matzkin et al. ACI Vol. LII

![Table 1](image-url)
prostate volume. Mean follow-up was 44 months (range 6-72 months). For this report, each patient filled, in average, 8 urinary questionnaires (IPSS) and 8 sexual function questionnaires (IIEF). Beyond the second year of follow-up, information about sexual function was gathered by free questions, including about general satisfaction and the use of drugs.

The change over time in urinary symptoms is presented in Table 2. To compare morbidity, this table contains data about 432 patients who were treated with brachytherapy alone (unpublished data). Severe deterioration occurs during the first year after treatment, with improvement and return to baseline values toward the end of the first year and even further improvement toward the end of the second year. All patients received alpha-adrenergic antagonists soon after treatment and continued as required. Two patients had refractory urinary retention after treatment and required an indwelling urethral catheter for few months, after which it was removed with no need of TUR-P. Another patient required prostate resection due to severe urinary symptoms. His postoperative period was benign. One patient suffered from intermittent hematuria which required complete investigation, and was related to radiation damage. The hematuria resolved spontaneously. None of the patients have suffered from urinary incontinence following treatment. One patient had diarrhea and mild rectal bleeding after the end of the external radiation sessions. Both diarrhea and bleeding resolved after a month of local treatment with Proctofoam. One patient suffered from perianal burning sensation, without any signs of inflammation.

Out of the study group, only 34 patients (55%) were sexually active before treatment. This relatively low rate can be explained by the patients’ age and by the assumption that patients with normal sexual function might have not been choosing a combination therapy with androgen deprivation which causes, at least temporarily, unavoidable decrease in sexual function. During the first year after treatment, 32 of the patients with good sexual function have suffered from sexual dysfunction and particularly from a decrease in libido (partially under the influence of androgen deprivation treatment). Treatment with sildenafil was given to 17 patients and 12 of them reported of improvement in the first year. At the end of the second year, 27 patients, from the patients who had any pre-treatment sexual function, reported satisfying sexual function. Mean PSA levels over time, including median and range values, are presented in Table 3. PSA increase, which is defined as treatment failure by the ASTRO definition, was seen in 3 patients. One of them was treated successfully with cryotherapy, with PSA levels less than 0.2 ng/ml in the last follow-up visit and with no urinary incontinence. The second one is treated with permanent androgen deprivation therapy with good results and the third older one (81 years) is being followed with watchful waiting.

### DISCUSSION

Permanent interstitial brachytherapy as treatment for localized prostate cancer is an accepted treatment modality and is used more frequently over the last decade. Combination of two radiation modalities, permanent interstitial brachytherapy and external beam radiotherapy, is not required in patients with good prognostic factors such as serum PSA level less than 10, good to moderate cell differentiation (i.e., Gleason score less than 7), and clinical stage of T1-T2a. On the other hand, local treatment alone, however successful and effective, does not result in high cure rates in patients with Gleason score 8-10, since the chance that the disease is localized within the prostate in these patients is small. Even a combination of internal and external radiation in these patients is not sufficient for good cure rates for the same reason: the risk of metastatic disease, at least microscopically, is extremely high.

Patients chosen by us for combination therapy are those with moderate prognostic factors, mostly Gleason score 7. PSA above 15 ng/ml or clinical stage T2b are also considered moderate prognostic factors and thus justify the use of combination therapy. This group carries the chance of

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tr>
<td><strong>IPSS BEFORE AND AFTER TREATMENT (maximal follow-up 24 months)</strong></td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
</tr>
<tr>
<td>Time(months)</td>
</tr>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>Mean IPSS</td>
</tr>
<tr>
<td>Median IPSS</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>TABLE 3</th>
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<tr>
<td><strong>PSA CHANGE OVER TIME</strong></td>
</tr>
<tr>
<td><strong>Time (month)</strong></td>
</tr>
<tr>
<td>No of patients</td>
</tr>
<tr>
<td>Mean PSA</td>
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<tr>
<td>Median PSA</td>
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</table>
periprostatic disease, which can be demonstrated in up to 40%. Combination therapy with internal and external radiation enables higher localized radiation levels than can be administered by external beam radiotherapy alone, and therefore is probably more effective. Control over local prostate disease is the basis of radical therapy. Experience gained over many years in Memorial Sloan Kettering indicates that local disease which remains after radical therapy will eventually lead to spreading of the disease until the patient’s death. This is the rationale behind external radiation dose escalation, a popular modality which is possible thanks to improvements in radiation equipment and its accompanied computerization. The basic assumption is that there is a direct link between radiation levels administered and the ability to control the tumor. Combination of permanent interstitial brachytherapy and external beam radiotherapy enables administration of the maximal radiation dose. Although there are different methods of combination therapy, the ideal combination and the timing of internal and external radiation administration still have not been decided. Among others, the main reasons are lack of prospective and comparative data between different methods and relatively short and different follow-up periods. Combination therapy can provide synergistic rather than additive influence.

Addition of androgen deprivation therapy to patients with moderate prognostic factors is based on accumulative data from the USA and Europe, and it becomes the standard of care in these patients. Search in contemporary literature reveals that androgen deprivation therapy is administered for periods of 6 months up to 2-3 years, still without any evidence-based preference. We chose a combination according to Stone et al of 6 months of androgen deprivation therapy (neoadjuvant and adjuvant), during which internal and external radiotherapy was administered.

The reported results of combination radiotherapy in the treatment of patients with moderate prognostic factors are very satisfying. PSA-based biochemical control indicates complete remission in 80-85% of the patients for 5-10 years (Table 4). These results are better than reported results of external beam radiotherapy or radical prostatectomy.

We defined this group and the preferred treatment option since the beginning of application of brachytherapy in Israel, seven years ago. All patients with Gleason score 7, PSA less than 20 and clinical stage T1-T2b were included in this group. We adopted the combination therapy modality according to Stone, and followed these patients prospectively with validated questionnaires for urinary and sexual disorders while using PSA as an index to success.

Although the follow-up was relatively short and the study group was not large, this study is unique in its well-defined inclusion criteria and meticulous follow-up. From our experience, moderate-to-severe rectal complications were not seen despite the combination of the two radiation modalities, different from what is reported following external radiation alone. Mild rectal morbidity was easy to treat and reversible within a year at the most. Urinary disorders, mostly irritative, were observed, but not more prevalent than in patients treated with brachytherapy alone. In our study, there were no significant IPSS changes when compared to patients who were treated with brachytherapy alone. Therefore, combination therapy of internal and external radiotherapy does not increase lower urinary tract morbidity. There was no incidence of urinary incontinence in these patients, but there were certainly urgency and frequency which justified the use of medica-

<table>
<thead>
<tr>
<th>Authors</th>
<th>No of patients</th>
<th>Median follow-up (months)</th>
<th>Treatment failure definition</th>
<th>Time point (years)</th>
<th>Survival free of disease by biochemical definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lederman et al, 2001</td>
<td>114</td>
<td>44</td>
<td>Two increases ≥0.5 ng/ml which lead to PSA ≥1ng/ml</td>
<td>6</td>
<td>75%</td>
</tr>
<tr>
<td>Critz et al, 2003</td>
<td>144</td>
<td>48</td>
<td>PSA&gt;0.2ng/ml</td>
<td>5</td>
<td>75%</td>
</tr>
<tr>
<td>Sylvester et al, 2003</td>
<td>232**</td>
<td>66</td>
<td>Two increases in PSA</td>
<td>10</td>
<td>77%</td>
</tr>
<tr>
<td>Dattoli et al, 2003</td>
<td>161</td>
<td>84</td>
<td>PSA&gt;0.2ng/l</td>
<td>10</td>
<td>79%</td>
</tr>
<tr>
<td>Radge et al, 2000</td>
<td>75</td>
<td>122</td>
<td>Two increases in PSA</td>
<td>10</td>
<td>79%</td>
</tr>
<tr>
<td>Hiratsuka et al, 2004</td>
<td>25</td>
<td>44</td>
<td>3 increases in PSA after the nadir</td>
<td>5</td>
<td>96%</td>
</tr>
<tr>
<td>Stevens et al, 2003</td>
<td>47</td>
<td>36</td>
<td>Two increases in PSA</td>
<td>3</td>
<td>91%</td>
</tr>
</tbody>
</table>

*Moderate prognostic factors: 1) clinical stage T2b-T2c; 2) Gleason score 7; 3) PSA between 10 and 20 ng/ml
**The original reference does not indicate how many from the 232 patients were with moderate prognostic factors

TABLE 4
SUMMARY OF REPORTED RESULTS OF PATIENT WITH MODERATE RISK FACTORS* WHO WERE TREATED WITH COMBINATION THERAPY
tions, such as alpha-adrenergic antagonists, for symptomatic relief.

Reports in the English literature on complications after combination therapy are limited. Sarosdy\textsuperscript{29} reported especially worse results in 61 patients. Sixteen percent (16\%) had urinary retention after treatment and most of them required surgery for removal of obstructive tissue. Thirty-six percent (36\%) underwent investigation due to rectal bleeding, some of them required coagulation of bleeding vessels, and 4 patients required intestinal diversion due to local complications. The majority of the reports describe much lower complications rates, most of them are mild, similar to our experience. Stevens et al\textsuperscript{27} described only 6\% out of 82 patients with significant urinary disorders, and only one patient required surgery for removal of obstructive tissue. Hiratsuka et al\textsuperscript{26} described only one out of 72 patients with severe urinary side effects. These large differences between the above quoted studies are derived not only from different seeds implantation techniques, but also from different patients' selection and drug therapy after radiotherapy.

This modality does not lack side effects regarding sexual function. Among others, the androgen deprivation therapy given for 6 months causes decrease in libido and potency, at least for one year since the onset of treatment. Thus, effects of treatment should be measured at least one year after the onset of androgen deprivation therapy. Our experience demonstrates decrease in potency. Nevertheless, patients responded to 5-PDE inhibitors. Overall, 80\% of those who were sexually active before treatment remained with a satisfying sexual function, either spontaneously or with the aid of medications such as sildenafil. Our data are better than data published elsewhere about sexual dysfunction after other treatment modalities in localized prostate cancer, such as radical prostatectomy and external beam radiotherapy\textsuperscript{30}.

Regarding the most important results for the patient and for evaluating this treatment modality: the chance for cure and the probability for recurrent PSA increase, our results are most encouraging. Only 3 out of 64 patients were defined as treatment failure. One should examine the good results in this study group while paying attention to two aspects. One, the patients in this study group had moderate prognostic factors, and therefore had chances for cure which were not favorable to begin with. Second, the follow-up time was relatively short – less than 4 years. In prostate cancer specifically, this period is too short to discuss disease-free state, especially regarding the fact that PSA levels in the first year or so were artificially low due to the short-term androgen deprivation therapy administered to all patients.

CONCLUSION

Our experience, similar to that described in the literature, demonstrates that the treatment modality which combines permanent interstitial brachytherapy and external beam radiation therapy with short-term androgen deprivation therapy results in encouraging outcome patients with moderate prognostic factors. There were no unusual side effects with this treatment and certainly not more than with any of the radiation modalities when used alone. The early results of biochemical surveillance of PSA levels indicate high rates of disease-free state. This combination therapy should be offered to patients with intermediate risk factors as a treatment option, in addition to therapeutic options available at the present.

SUMMARY

Kombinacija permanentne intersticijelne brahiterapije bazirana na radioaktivnom jodu sa spoljnom zračnom terapijom je alternativa drugim metodama lečenja, kao što je radikalna prostatektomija ili spoljna zračna terapija pojedinačno kod bolesnika sa srednjim rizikom koji imaju lokalizovani karcinom prostate. U ovom radu iznosimo naše iskustvo sa ovom kombinovanom terapijom.


Zaključak: Kombinacija permanentne intersticijelne brahiterapije i spoljašnjeg zračenja u odgovarajućih bolesnika nije uzrok dodatnog morbiditeta i njihovi biohemjski rezultati odobravaju njihovu primenu. Ovaj modalitet lečenja može biti ponuđen i prihvaćen kao dobra alternativa drugim radikalnim terapijskim opcijama, bolesnicima koji imaju karcinom prostate sa umerenim rizikom.

Ključne reči: karcinom prostate, brahiterapija, spoljašnja zračna terapija.

REFERENCES


