

## MANAGEMENT OF LOCALIZED PROSTATE CANCER

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The subject of management for localized prostate cancer is complicated due to the heterogeneity of the disease, and co-morbid conditions in an often elderly population. There are many management options, including watchful waiting with serial measurement of PSA, hormonal blockade, Radical Prostatectomy (RP), Nerve Sparing RP, Cryosurgery, Laparoscopic RP, Robotic RP, External Radiation Therapy (XRT), Proton Beam XRT, Intensity Modulated Radiation Therapy (IMRT), permanent seed Low Dose Rate (LDR) radiation implant, and temporary seed High Dose Rate (HDR) radiation implant. The gold standard in medicine to test the relative pros and cons of these different treatments is the randomized trial. Remarkably, no modern randomized trials exist in the PSA era. Fortunately, prostate cancer is rarely an emergent condition. Therefore, patients have time to carefully review the subject, reach a comfort zone, and make the decision which makes the most sense to them.

While the American Cancer Society estimated that there would be 230,110 newly diagnosed prostate cancer cases in 2004, only about 29,900 will die of the disease [1]. Therefore, a good case can be made for observation in many patients. The factors to consider for observation include the biology of the disease, and general life expectancy of the patient independent of prostate cancer. Specifically, patients with early stage disease, low grade pathology, and low PSA, are likely to have slowly progressive disease. Patients who are elderly, or with significant co-morbid conditions may be safely watched, regardless of the biology of the disease. The key is patient selection. There is a wide variation of mortality from prostate cancer with watchful waiting, depending on the series, as shown in the table below [2-7] :

### PROSTATE CANCER DEFERRED MANANGEMENT, OR WATCHFUL WAITING

<u>AUTHOR</u>	<u>#PTS</u>	<u>MORTALITY FROM PROSTATE-CANCER</u>	<u>F/U</u>
George [2]	152	4%	7 years
Chodak [3]	828	5%	5 years
Johannson [4]	223	10%	12 years
Adolfson [5]	172	12%	7 years
Chodak [3]	828	17%	10 years
Handley [6]	278	42%	5 years
Kattan [7]	2,446	30%	12 years

In the George paper, patients had early stage disease, and low grade lesions. Mortality from prostate cancer was only 4%. Handley et al, reported on patients with more advanced disease, and high grade histology. Prostate cancer mortality was much higher, at 42%. The Chodak papers showed a 5% mortality at 5 years, which increased to 17% at 10 years. Therefore, patient selection is critical in determining who should receive treatment. The largest study on watchful waiting was conducted in the United Kingdom [7]. A total of 2,446 patients with clinically localized prostate cancer were studied. Within 6 months of diagnosis, 30% were treated with Hormonal Blockade. At 12 year

follow-up, 30% of the patients had died of prostate cancer.

Management options for localized prostate cancer include, including watchful waiting with serial measurement of PSA, hormonal blockade, RP, Nerve Sparing RP, Cryosurgery, Laparoscopic RP, Robotic RP, XRT, Proton Beam XRT, IMRT, permanent seed LDR radiation implant, and temporary seed HDR radiation implant. RP and XRT have a long-term proven curative track record. The National Institutes of Health Consensus Panel concluded in 1988 that 10 year survival was comparable with either treatment [8]. However, this was in the pre-PSA era. Now, the controversy revolves around PSA measured disease free survival. In comparing multiple retrospective series of patients with clinical stage T1/2 disease, 5 year PSA disease free survival is ~ 70% with either RP or XRT. The American Urological Association convened a Prostate Cancer Clinical Guidelines Panel in 1995, and concluded, "data from the literature do not provide clear-cut evidence for the superiority of any 1 treatment [9]." For pathologically organ confined prostate cancer, 5 year PSA disease free survival is ~ 90%. These data exclude patients who are found to have pathologic stage T3 disease. When all patients with clinical stage T1/2 disease are included, the 5 year PSA disease free survival is ~ 70%. Nilsson et al, from the Department of Oncology and Pathology at the Karolinska Institute in Stockholm Sweden, performed an extensive review of the medical literature on prostate cancer, encompassing 152,614 patients, one meta-analysis, 30 randomized trials, 55 prospective trials, and 210 retrospective studies [10]. They reached several conclusions, including :

1. There is substantial evidence that patients with low risk prostate cancer, PSA  $\leq$  10, Gleason Score  $\leq$  6, and clinical stage  $\leq$  T2b treated with either external radiation therapy, radiation implant, or surgery have similar outcomes.
2. There is fairly strong evidence that patients with intermediate and high risk prostate cancer (PSA  $\geq$  10, Gleason Score  $\geq$  7, and clinical stage  $>$  T2), i.e. patients not normally suited for surgery, benefit from higher than conventional dose.
3. Post-operative XRT after radical prostatectomy in patients with pathologic T3 disease, prolongs biochemical DFS, and that the likelihood of achieving long-term DFS is higher when XRT is given in an adjuvant, rather than a salvage setting.

In the largest study in the United States, Tward et al, reviewed prostate cancer specific mortality and any cause mortality in 60,290 men with organ confined prostate cancer identified in the National Cancer Institute's Surveillance Epidemiology and End Results Program [11]. The study period covered 1988-2002. The authors compared survival after surgery, brachytherapy, and no treatment. On univariate and multivariate analysis, there was no difference between surgery and brachytherapy. Both were significantly superior to no treatment.

In reviewing data with different treatment strategies, it is critical to make sure that the patients are comparable. For example, among patients with T1/2 prostate cancer, patients with lower Gleason Scores have a more favorable prognosis than those with higher Gleason Scores, regardless of treatment, as shown in the following table [12,13] :

PSA 5 YEAR DISEASE FREE SURVIVAL GLEASON BY SCORE		
<u>TREATMENT</u>	<u>2-6</u>	<u>7-10</u>
RP [11]	70%	30%
XRT [12]	69%	35%

Similar variation occurs with PSA. Therefore, the comparative groups in question should have similar T-Stage, Gleason Scores, and PSAs. Then, an unbiased treatment result comparison is more valid. The best case of course, is the randomized trial.

Currently, there are no randomized data in the PSA era to compare disease free survival after RP versus high dose XRT (6840 cGy in 38 fractions). There are now a number of single institution comparisons. The Cleveland Clinic compared 354 patients who had undergone RP, to 253 patients who underwent high dose XRT [14]. All patients had T1/2 prostate cancer. Patients were comparable in regard to Gleason Score and PSA. The 5 year PSA disease free survival was 76% in patients undergoing RP, and 75% treated with high dose XRT. In the second study, Harvard and Pennsylvania, compared 332 patients who underwent RP to 197 patients treated with high dose XRT [15]. Again, the patients were comparable in regard to prognostic factors. All patients had Stage T1/2a, Gleason Score < 7, and PSA < 10. The 5 year PSA disease free survival measured 84% in patients who had undergone RP, compared to 89% for those who received high dose XRT. The better survival figures reported in the second study may be explained by the fact that these patients had more favorable disease, i.e. patients with T2b/c, and Gleason Score > 7, were excluded.

The Cleveland Clinic recently updated their experience, comparing patients who underwent RP, low dose XRT, or high dose XRT, for T1/2 prostate cancer [16]. The results appear in the following table :

T1/2 PROSTATE CANCER  
CLEVELAND CLINIC  
8 -YEAR FOLLOW-UP

<u>TREATMENT</u>	<u>#PTS</u>	<u>PSA-DFS</u>	<u>P-VALUE</u>
RP	795	56%	-
Low Dose XRT	509	53%	-
High Dose XRT	222	93%	< 0.001

The following data compare single institution data in patients with T-1/2, PSA  $\leq$  10, Gleason Score  $\leq$  6 prostate cancer, who underwent RP vs. XRT [17] :

T1/2 PROSTATE CANCER  
PSA  $\leq$  10, Gleason Score  $\leq$  6  
PSA DFS

<u>AUTHOR</u>	<u>#PTS</u>	<u>RP</u>	<u>XRT</u>	<u>F/U</u>
D'Amico [18]	627	84%	89%	5 yrs
Keyser [14]	460	76%	75%	5 yrs
Kupelian [19]	226	80%	81%	5 yrs
Martinez [17]	382	67%	69%	7 yrs

Proton beam radiation therapy is another form of XRT. Clinical outcomes have not been significantly better than with XRT. Schulte et al, reported on a series of 911 patients with limited Stage prostate cancer treated with proton beam at Loma Linda University [20]. The 5 year PSA DFS was 82% at 5 years. Grade 2 rectal complications were reported in 3.5% of patients. Grade 2 bladder complications were noted in 5.4%. Investigators at Harvard conducted a clinical trial, in which patients

were randomized to Proton Beam or XRT. There was no difference in overall survival or disease free survival, and morbidity was significantly worse in the Proton Beam patients [21]. The survival and complication data are shown in the following two tables below :

PROTON BEAM VS. XRT  
HARVARD RANDOMIZED TRIAL  
SURVIVAL

<u>TREATMENT</u>	<u>#PTS</u>	<u>OS</u>	<u>DFS</u>
Proton Beam	103	75%	39%
XRT	99	80%	41%

PROTON BEAM VS. XRT  
HARVARD RANDOMIZED TRIAL  
COMPLICATIONS

<u>COMPLICATION</u>	<u>PROTONS</u>	<u>XRT</u>
Rectal Bleeding	32%	12%
Urethral Stricture	17%	7%
Transient Hematuria	14%	6%
Chronic Hematuria	2%	2%
Urinary Incontinence	1%	1%
Sexual Dysfunction	60%	63%

Finally, the Loma Linda Nursing Group studied quality of life outcomes in 185 patients at Loma Linda University treated with Proton Beam, XRT, Radical Prostatectomy, and Watchful Waiting [22]. No difference in quality of life was found.

Regarding patients under the age of 60 years, there has been a bias that results with XRT are poor. Until recently, few data exist in the PSA era regarding outcome with XRT in this patient subset. At least 5 series have reported good results in younger men with prostate cancer, treated with XRT. Stanford reported XRT results in 48 patients < 60 years of age with Stage T1/2 prostate cancer. With a median follow-up of 14.6 years, PSA disease free survival was 71% [23]. These data compare very favorably to patients > 60 years of age, and to radical prostatectomy data as noted above. Similar results have been reported by other investigators. Konski et al, from the University of Pennsylvania reported similar results in a series of 84 patients  $\leq$  55 years of age treated with XRT [24]. They reported 82% 5 year PSA disease free survival, which was comparable to age matched controls between the ages of 60 to 70, and  $\geq$  70 years. Freedman et al, reported 5 year PSA disease free of 89% in men < 65 treated with XRT, vs. 84% in men > 65 [25]. Zelefsky et al, reported 79% PSA disease free survival in 96 men  $\leq$  60 treated with XRT, vs. 78% in 644 men > 60 [26]. Johnstone et al, reviewed data from the Department of Defense Center for Prostate Disease Research treated with XRT between 1988 and 2000 at Department of Defense facilities [27]. No difference was found in patients < 60 vs.  $\geq$  60 years of age. Finally, Tward et al, compared 1,233 men < 60 years old treated with brachytherapy, to 11,566 men who underwent radical prostatectomy between 1988-2002 from the SEER data base [11]. Ten year actuarial survival curves showed no difference in prostate cancer specific mortality and any cause mortality.

XRT results have been criticized, because of late recurrences. However, PSA disease free survival also declines after RP as shown in the following table :

PSA DISEASE FREE SURVIVAL AFTER RP  
STAGE T-1/2 PROSTATE CANCER

<u>INSTITUTION</u>	<u>#PTS</u>	<u>5 YRS</u>	<u>10 YRS</u>	<u>15 YRS</u>
Mayo Clinic [28]	3,170	77%	54%	40%
UCLA [29]	601	69%	47%	-
Washington [30]	925	76%	62%	-
Duke* [31]	322	82%	70%	55%

\*The last series from Duke is especially interesting in that these patients all had organ confined disease. In this study, 613 patients underwent RP for clinical Stage T-1/2 disease. On pathology evaluation, 53% (322/613) had organ confined disease. From the above data, it is quite clear that even patients with organ confined disease have PSA failures after surgery. This is due mostly to occult metastatic disease present at diagnosis not detectable by current means.

The same problem occurs after XRT. Unfortunately, there are still no randomized trials to compare results after RP and XRT. The best single institution data comes from the Cleveland Clinic, which shows a drop in PSA disease free survival with increasing follow-up after both RP and XRT, as shown in the following table :

T-1/2 PROSTATE CANCER  
CLEVELAND CLINIC : RP VS. XRT  
8-YEAR FOLLOW-UP

<u>TREATMENT</u>	<u>#PTS</u>	<u>5 YRS</u>	<u>8 YRS</u>
RP	795	76%	56%
Low Dose XRT	509	75%	53%
High Dose XRT	222	97%	93%

Finally, on the subject of management of localized treatment, radiation implants are being done with increasing frequency across the United States. Swedish Hospital in Seattle recently reported data on 126 patients with T1/2 prostate cancer who underwent permanent I-125 radioactive seed implantation [32]. The patients had favorable T1/2 disease, in that they had median PSA of 5.0, and Gleason Scores  $\leq 6$ . The Seattle Group reported 85% 10 year PSA disease free survival. These data are remarkably similar to the high dose XRT data from the Harvard and Pennsylvania report, noted above, i.e. 89% 5 year PSA disease free survival. Bladder and rectal complications are reported to be less with implants, than with high dose XRT or surgery. There was no incontinence in patients with no prior TURP history. However, in patients with a previous history of TURP, urinary incontinence occurred in 12.5%. Preservation of sexual function appears to be higher with implants. The following data have been reported with I-125 (+/- low dose XRT) permanent seed implant :

STAGE T-1/2 PROSTATE CANCER  
RESULTS WITH I-125 IMPLANT

<u>AUTHOR</u>	<u>#PTS</u>	<u>PSA-DFS</u>	<u>F/U</u>
Grimm [32]	126	85%	10 yrs
Priestly [33]	130	76%	2.5 yrs
Wallner [34]	92	60%	2 yrs
Blasko [35]	226	78%	5.5 yrs
Critz [36]	303	79%	5.5 yrs
Dattoli [37]	73	79%	2 yrs
Potters [38]	1,504	78%	6 yrs
Stock [39]	1,510	76%	6 yrs
Torres [40]	466	85%	5 yrs

The Seattle Group also uses High Dose Rate (HDR) implant technique, with Ir-192 temporary afterloading. The technique is done in combination with a lower dose of XRT (4500 cGy). The data from the HDR technique parallel the I-125 results. Eulau et al, reported on 104 patients with T1c-T3c disease, median PSA 8.1, and all Gleason Scores (2-10) treated with low dose XRT + HDR technique [41]. Therefore, this series included patients with less favorable disease than the I-125 series noted above. There were patients with T3 disease, higher PSAs, and higher Gleason Scores. Yet, the 10 year actuarial PSA disease free survival was 78%, quite similar to the data reported above in more favorable patients. Complications with low dose XRT + HDR were quite similar to I-125, i.e. low rates of urinary and rectal complications with HDR. Previous TURP did not correlate with incontinence with HDR. This could be explained by the ability to tailor urethral doses with HDR. This can not be done as easily with I-125.

HDR data compare favorably to surgery, high dose XRT, and I-125, and have been achieved in patients with locally advanced disease, with no Gleason Score or PSA exclusions, as shown in the following table [41-47, 73] :

LOCALIZED PROSTATE CANCER  
RESULTS WITH HDR IMPLANT

<u>INSTITUTION</u>	<u>#PTS</u>	<u>STAGE</u>	<u>GLEASON SCORE</u>	<u>Dx PSA</u>	<u>PSA DFS</u>	<u>F/U</u>
Seattle [41]	104	T1b-T3c	4-10	8.1	78%	10 yrs
Beaumont [42]	128	T2a-T3c	4-10	30.4	76%	2 yrs
Humboldt [43]	58	T2b-T3c	4-10	14.0	85%	3 yrs
Goteborg [44]	50	T1-T3	4-10	9.0	84%	4 yrs
Kiel [45]	131	T1b-T3c	4-10	25.0	75%	8 yrs
Lahey [46]	52	T1-2	7-10	nr	90%	1 yr
Long Beach [47]	200	T1c-T3c	4-10	nr	95%	2 yrs
JACC [73]	109	T1c-T3c	4-10	8.6	89%	5 yrs

With respect to the two implant techniques, HDR offers some significant advantages over I-125, and other permanent seed (e.g. Pd-103) techniques. Firstly, HDR is a temporary seed placement technique. With the permanent seed I-125 or Pd-103 procedures, the patient is permanently implanted with ~ 100 seeds. Therefore, the patient goes home radioactive, with radiation exposure to family members and others. With HDR, the patient goes home with no radiation inside them. Secondly, with the permanent seed techniques, seeds can migrate in the prostate after implant, resulting in dose inhomogeneity. In addition, seeds can leak out of the prostate into the bladder, or into the bloodstream. Seeds have been known to embolize to the lung and heart [48]. HDR is a closed system with a blind end needle, so the seed can not escape. Thirdly, HDR allows much more flexibility in tailoring tight dose distributions to the bladder, rectum, and especially, the urethra. This has resulted in a much lower incidence of urethritis and urinary retention with HDR, than with permanent seeds. Fourthly, HDR can treat extraprostatic extension better than the permanent seed techniques. Fifthly, pubic arch interference and large prostate size ( $\geq 60 \text{ cm}^3$ ) create such technical difficulties with Permanent Seed implants that these patients are excluded. HDR Implant can be done in these patients. Finally, the permanent seed technique calls for a pre-plan, which is not always matched by the real implant. Again, dose inhomogeneity can result. HDR is a real time treatment planning technique.

There are at least two studies comparing HDR Implant to LDR Implant alone [49,50]. Wang et al, compared 108 HDR implant cases to 72 LDR cases [49]. Eleven different radiation dose planning end points were compared. HDR was statistically superior in all 11. For example, the maximum dose to the urethral was 127% in the HDR cases vs. 207% with LDR. The maximum dose to the rectum was 100% with HDR vs. 180% with LDR. Grills et al, reported less rectal and urinary complications with HDR vs. LDR in a review of 65 HDR cases and 84 LDR cases [50].

The Seattle Group protocol calls for implant alone in patients with favorable disease, i.e. with low likelihood of extracapsular spread and lymph node involvement. With less favorable disease, but still considered localized, the group advises low dose XRT plus implant. The addition of low dose XRT is based on treating periprostatic tissues, including the seminal vesicles. The protocol calls for 4500 cGy XRT + Implant. Patients with > 30% risk of extraprostatic extension, as defined by the Partin Nomogram, have been treated according to this protocol. Recent data indicate that implant alone may be as effective.

Standard management with HDR, has been HDR Implant x 1 + XRT x 5 weeks. However, there is no conclusive evidence that the added XRT improves outcome. Indeed, there are now several large series which have shown no benefit. Blasko et al, reviewed the results of 634 prostate cancer patients who underwent Implant +/- XRT treated in Seattle [51]. There was no significant difference in PSA survival. Patients were subdivided into low risk, intermediate risk, and high risk, based on T-Stage, Gleason Score, and PSA. No survival difference was found in any patient subgroup. Notably, there was increased rectal morbidity in the patients undergoing Implant + XRT (8%) vs. Implant alone (2%). Blasko concluded, "Although the addition of XRT to brachytherapy is conceptually appealing for patients with higher risk prostate carcinoma, we were unable to demonstrate a benefit." Grado et al, also have reported no difference in PSA survival in a series of 490 patients treated with Implant, Implant + XRT, or Implant + Hormonal Blockade [52]. Kupelian et al, recently performed a multi-institution review, which included data from M.D. Anderson, Memorial Sloan Kettering, and the Cleveland Clinic [53]. The study included 1,172 patients who underwent Implant +/- XRT. There was no difference in 5 year PSA disease free survival. Merrick et al, reviewed their experience in 413 patients who received Implant +/- XRT [54]. Once again, adding supplemental XRT provided no significant survival advantage. Potters et al, from Memorial Sloan Kettering, reported 12 year outcome on 1,504 patients who underwent Implant +/- XRT [55]. Once more, no survival advantage was found with the addition

of XRT. Finally, Stock et al, reviewed 1,510 patients treated at Mount Sinai Hospital with Implant +/- XRT [56]. Median follow-up was 6 years. Again, supplemental XRT provided no survival benefit.

Regarding complications, Chen et al, reviewed 5,621 men undergoing Implant +/- XRT from 1991 to 1999, registered in the National Cancer Institute's Surveillance Epidemiology and End Results Program [57]. In this series, 60% of patients had Implant + XRT, which caused significantly increased complications to the bladder and rectum compared to Implant alone. Lee et al, reviewed the RTOG multi-institutional cooperative trials, RTOG 0019, 9406, 9509, and 9805, which compared Implant +/- XRT and XRT alone [58]. The addition of XRT caused significantly higher complications to the bladder and the rectum. Therefore, based on the preceding paragraphs, Implant + XRT has failed to improve PSA measured disease free survival while increasing complications, compared to Implant alone. Therefore, a case can be made for HDR Implant alone.

Over the past 4 years, we have presented our results with HDR Implant +/- IMRT, at a number of national and international meetings, including the Radiologic Society of North America, American Radium Society, American Society of Clinical Oncology, American Society of Therapeutic Radiation Oncology, American Brachytherapy Society, and the European Society of Therapeutic Radiation Oncology [59-79]. Most recently, we presented our data in 201 patients with Stage T1/2 patients treated with HDR Implant alone at the Annual Meeting of the European Society of Therapeutic Radiation Oncology, in Montpellier, France, in May 2007 [77]. With a median follow-up of 78 months (range : 6 months to 112 months), the PSA disease free survival was 89.1% (179/201) with HDR Implant alone. There were no Gleason Score or PSA exclusions. Long-term complications were minimal, with urinary stricture in 5.4%, urinary stress incontinence 4.0%, and chronic RTOG rectal symptoms 3.5%. These results compare favorably to surgery, XRT, IMRT, and permanent seed Implant +/- XRT. Indeed, we have compared our results in 201 HDR Implant patients to a series of 109 patients treated with HDR Implant + IMRT x 5 weeks [78]. With a median follow-up of 78 months, the PSA disease free survival was 89.1% (179/201) with HDR Implant alone vs. 88.1% (96/109) with HDR + IMRT [78]. The result was not statistically significant ( $p=0.6$ ). RTOG late rectal toxicity was higher in patients undergoing HDR + IMRT, with 15.6% (17/109) of patients experiencing Grade 2 and Grade 1 symptoms vs. 3.5% (7/201) receiving HDR alone ( $p<0.01$ ).

Four other studies have reported excellent results with HDR Implant alone. Gustafson et al, reported on a selected series of 132 favorable prognosis patients [80]. Patients had Stage T1/2 disease, Gleason Score  $\leq 6$ , and PSA  $\leq 10$ . With a median follow-up of 2.3 years, the PSA disease free survival was 98%. Morbidity was minimal, with 4% urethral stricture, 0% urinary incontinence, and 0% chronic rectal toxicity. Schour et al, also reported on 117 favorable prognosis patients, with Stage T1/2 disease, Gleason Score  $\leq 6$ , and PSA  $\leq 10$ . With a median follow-up of 2.1 years, the PSA disease free survival was 96%. Morbidity was again minimal, with 1% urethral stricture, and 1% chronic rectal toxicity [81]. Demanes et al, recently reported that HDR Implant alone is equivalent to HDR Implant + XRT for early prostate cancer [82]. They compared 117 patients with T1-2, PSA  $\leq 15$ , and Gleason Score  $\leq 7$  prostate cancer treated with HDR alone to an identical matched pair group treated with HDR + XRT. With a median follow-up of 40 months, the PSA disease free survival was 97% in both groups. Corner et al, reported on 109 patients with locally advanced or high grade prostate cancer treated with HDR monotherapy [83]. The median PSA was 15. With a median follow-up of 19 months, the PSA disease free survival was 100%. However, 51% of the patients are receiving adjuvant hormonal blockade. RTOG Grade 3 bladder toxicity was seen in 2%, and RTOG Grade 2 bowel toxicity in 1% of the patients.

Clearly, the preceding paragraphs challenge the idea that adding supplemental XRT to implants is necessary. Practicing Radiation Oncologists who do radiation implants, have increasingly dropped the addition of XRT. Lee et al, conducted a Patterns of Care Study on Prostate Cancer 36,496 patients

treated at 59 facilities in the United States in 1999 [84]. More than 50% of these patients were treated with Implant alone.

As noted earlier, there appears to be a benefit to adding Hormonal Blockade to XRT in patients with locally advanced prostate cancer. It is not yet known whether patients treated with HDR benefit from supplemental Hormonal Blockade. Martinez et al, reviewed the results of 1,260 unfavorable prostate patients treated at three institutions with a protocol calling for HDR + XRT +/- Hormonal Blockade [85]. Unfavorable was defined as Gleason Score  $\geq 7$ , PSA  $\geq 10$ , or clinical Stage  $\geq T2b$ . The 8 year PSA disease free survival was 85% with Hormonal Blockade vs. 81% without, a difference which was not statistically significant.

The Partin Nomogram is helpful in tailoring individual treatment plans. The Partin Nomogram was constructed by pathologists from the University of Michigan, Baylor, and Johns Hopkins [86]. The study reviewed 4,133 men who had undergone RP for what had been judged to be clinically localized prostate cancer. On pathologic analysis, only 48% of the specimens were found to be organ confined cancers. Therefore, 52% of the patients who underwent radical prostatectomy had tumor outside the prostate. Thru the presenting clinical stage, PSA, and Gleason Score, Nomogram tables were constructed that allowed accurate prediction of pathologic extraprostatic tumor extension. This data can now be used to help a patient's prospective management decision. If a patient has a high risk of extraprostatic extension, he may decide against RP, which can not clear extraprostatic tumor.

As noted above, the Partin study showed, 52% of men who undergo RP will have tumor outside the prostate. Not surprisingly, these men are at higher risk for tumor recurrence. Historically, the use of adjuvant XRT in these cases was controversial. This was due to several factors. Firstly, the data were retrospective. Therefore, selection bias effected decisions in whether or not to give adjuvant XRT. Generally, the patients receiving XRT had more extensive pathologic Stage C (T3) disease, and higher Gleason Scores. Therefore, they had worse prognoses independent of XRT. Patients referred for XRT often had higher pathologic stage, greater incidence of seminal vesicle involvement, and higher pre-operative PSAs.

In order to answer the true benefits of adjuvant XRT in pathologic Stage C (T3), randomized trials were needed. Three randomized trials have now been published, by the EORTC, SWOG, and an Intergroup German Trial. All three showed a statistically significant improvement in PSA Disease Free Survival (DFS) when adjuvant XRT was given [87-89]. The following table summarizes these results :

PATHOLOGIC C (T3) PROSTATE CANCER  
RP vs. RP + XRT  
RESULTS OF RANDOMIZED TRIALS

<u>STUDY</u>	<u>#PTS</u>	<u>PSA DFS</u>		<u>FOLLOW-UP</u>
		<u>RP</u>	<u>RP + XRT</u>	
EORTC [87]	1,005	52%	72%	5 years
SWOG [88]	473		23%	47%
German [89]	385	60%	81%	4 years

The benefit of high dose XRT, vs. low dose XRT + Implant, has been analyzed in a randomized trial [90]. The Ontario Clinical Oncology Group conducted a study in 136 patients with locally advanced, clinical Stage T2b, T2c, and T3 prostate cancer. Patients were randomized to receive high dose XRT, vs. low dose XRT + Implant. The 4 year disease free survival was 49% in the high dose XRT group, compared to 67% in those receiving low dose XRT + Implant.

For patients with locally advanced T3 prostate cancer, results with surgery and high dose XRT

are poor, with ~ 25% 5 year PSA disease free survival. The addition of hormonal blockade to surgery or high dose XRT, may significantly improve survival. While hormonal blockade has not proven curative in metastatic prostate cancer, response rates and palliative benefits are often high. Therefore, investigators judged that it was logical to combine hormonal blockade with surgery or high dose XRT for patients with T3 disease, or high-grade pathology. Several randomized trials have demonstrated improved 5-year PSA disease free survival, and overall survival in patients with locally advanced, or high grade prostate cancer treated with high dose XRT + hormonal blockade compared to high dose XRT alone. The largest randomized trial involved 977 patients, and was conducted by the Radiation Therapy Oncology Group (RTOG). Patients were randomized to high dose XRT + hormonal blockade, or high dose XRT alone. The 5-year PSA disease free survival was 53% in patients receiving high dose XRT + hormonal blockade, compared to 20% with high dose XRT alone [91].

With respect to comparative complications with surgery and radiation, there is quite a reported range in the literature, as reported in the New England Journal of Medicine as shown in the following table [92] :

#### COMPLICATIONS OF CURATIVE TREATMENT FOR PROSTATE CANCER

<u>COMPLICATION</u>	<u>RADICAL PROSTATECTOMY</u>	<u>XRT</u>
Death	0.3-2%	0.2-0.5%
Incontinence	1-27%	1-3%
Urethral or Bladder Complications	10-18%	3-17%
Rectal Injury	1-3%	2-23%
Impotence	20-85%	40-67%

Because of this wide range of reported data, patient reported data may be more reliable. Such data has been published by the Medicare SEER study in the Journal of Clinical Oncology, and appears in the following table [93] :

#### PATIENT REPORTED COMPLICATIONS OF CURATIVE TREATMENT FOR PROSTATE CANCER

<u>COMPLICATION</u>	<u>RADICAL PROSTATECTOMY</u>	<u>XRT</u>
Urinary Incontinence	32%	7%
Impotence	56%	23%
Bowel	4%	10%

Several other investigator have published similar patient reported complications after Radical Prostatectomy, with the results shown in the following table :

#### PATIENT REPORTED COMPLICATIONS OF RADICAL PROSTATECTOMY FOR PROSTATE CANCER

<u>AUTHORS</u>	<u>URINARY INCONTINENCE</u>	<u>SEXUAL IMPOTENCE</u>	<u>URETHRAL STRICTURE</u>
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Kao [94]	33%	88%	21%
Augustin [95]	27%	86%	24%
Prowse [96]	59%	82%	15%

The newest radiation technique is called Intensity Modulated Radiation Therapy (IMRT). IMRT represents a significant advance beyond XRT. Radiation is still delivered externally, but by varying the intensity of the beam, the shielding, and gantry positions, much tighter radiation dosimetry has been achieved. The result is higher doses to the tumor, with improved sparing of normal tissues. The following table shows improved normal tissue sparing of bladder and rectum compared to XRT and 3 Dimensional Conformal Radiation Therapy (3D CRT) [97] :

RECTAL AND BLADDER EXPOSURE  
IMRT vs. 3D-CRT vs. XRT  
VOLUME : 90% PRESCRIPTION DOSE

<u>TREATMENT</u>	<u>RECTUM</u>	<u>BLADDER</u>
XRT	89%	76%
3D CRT	51%	52%
IMRT	6%	7%

This decreased volume of normal tissue exposure has translated into decreased morbidity, as shown in the following table [98] :

RECTAL BLEEDING AFTER IMRT VS. 3D-CRT  
MEMORIAL SLOAN KETTERING EXPERIENCE

<u>TREATMENT #PTS</u>	<u>RECTAL BLEEDING</u>
3D-CRT	61 10%
IMRT	171 2%

Chan et al, recently updated the MSK experience in these 171 IMRT patients [99]. The IMRT dose was 81 Gy, with 54% of patients receiving Hormonal Blockade. The 6 year PSA DFS was 78%. Chronic rectal bleeding occurred in 4% of patients, and 10% experienced Grade 2 urinary toxicity. The IMRT protocol calls for daily treatment for 8 weeks. Prior to each IMRT treatment a balloon is placed in the rectum. The balloon is then inflated to reduce dose to the rectum.

The preceding paragraphs have reviewed advances in delivering more tightly contoured radiation doses to the prostate, while minimizing dose to surrounding normal tissues. Technical advances have occurred in surgery as well. The following paragraphs summarize results with Cryosurgery, Laparoscopic Radical Prostatectomy (LRP), and Robotic Radical Prostatectomy (RRP).

Cryosurgery in prostate cancer treatment has a long history. Initially, the procedure was performed with liquid nitrogen, which resulted in a rapid freeze of the prostate. The technique was effective in eradicating cancer, but complications were significant due to lack of control of the rapid freeze. Recent years witnessed the development of a new technique to freeze the prostate, utilizing argon gas, which permits a slow, gradual freeze of the prostate. With argon gas, the prostate is frozen under transrectal ultrasound guidance. The ice ball can be stopped before it reaches the bladder and rectum. The technique has been generally accepted for use in the salvage of patients who have

developed locally recurrent prostate cancer after XRT. Chin and Touma conducted a recent review of the medical literature, and reported 40% 5 year PSA DFS with salvage cryosurgery [100]. The results with primary cryoablation of prostate cancer appear to be comparable to RP, XRT and radiation implants as shown in the following table [100-104] :

PROSTATE CANCER  
RESULTS WITH CRYOSURGERY AS PRIMARY TREATMENT

<u>AUTHOR</u>	<u>#PTS</u>	<u>DFS</u>	<u>F/U</u>
Bahn [101]	447	76%	5 years
Han [102]	106	75%	1 year
Donnelly [103]	76	79%	5 years
Aus [104]	54	39%	5 years

Complications with primary cryosurgery appear to be comparable to RP, XRT, and radiation implants. In the series reported by Han et al, from UCLA, complications included urinary incontinence (8%), urethral sloughing (5%), rectal discomfort (2.6%), and impotence (87%) [102]. Aus et al, from Sweden, reported urethral sloughing (15%), urethral strictures requiring surgery (15%), fistula (2%), and impotence (91%) [104].

Classically, RP has been performed via open surgical techniques. Recent years have witnessed less invasive techniques, including LRP and RRP. Akduman et al, conducted a review of the medical literature on LRP and compared the results to classic RP [105]. Follow-up is too short to make conclusions regarding PSA DFS. Hospitalization and recovery periods with LRP are shorter. The rates of positive surgical margins, urinary incontinence, impotence, rectal injury, urinary injury, and deep venous thrombosis appear to be comparable. With a median follow-up of 1 year in 1,000 patients who underwent LRP, Guillonneau et al, reported a 3 year actuarial PSA progression free probability of 90%, which is comparable to RP [106].

RRP was introduced in 2000. There are no long-term PSA follow-up data. Menon et al, reported their initial experience in more than 1,000 cases [107]. Results have been comparable to RP and LRP with respect to positive surgical margins and complications. El Hakim and Tweari reviewed performed a literature review of RRP, and reached similar conclusions [106]. Their final words on LRP and RRP, were “Although early results of minimally invasive treatment procedures are promising, long-term follow-up studies and survival data are necessary before these procedures can be considered first-line options for the treatment of prostate cancer.”

There are clearly many effective ways to deal with localized prostate cancer. The gold standard in medicine to compare treatments for a disease is the randomized trial. Remarkably, no randomized trials have been conducted to more precisely and fairly sort out the pros and cons of localized treatments for prostate cancer.

In the absence of randomized trials the preceding evidence suggests that the prostate does not have to be removed to gain long-term cure. The idea of organ conservation in cancer is not unique to prostate cancer. Randomized trials testing organ conservation with XRT exist in other organs, including breast cancer and laryngeal cancer. In the case of breast cancer, multiple randomized trials have been conducted around the world which have clearly demonstrated that limited surgery + XRT is equivalent to mastectomy [109-111], in regard to long-term survival, cure, and even local-regional recurrence. In 6 randomized trials summarized in the New England Journal of Medicine with 10 year follow-up, there was an aggregate rate of 7% chest wall and regional node recurrence after mastectomy, compared to 8% after breast conservation [109]. The NSABP reported the same conclusions with 20 year follow-up

[110]. Based on all of the preceding data, the National Institutes of Health convened an expert panel which discussed breast cancer in 1992 [111]. They issued a consensus statement, which read,

“Breast Conservation Treatment is an appropriate method of primary therapy for the majority of women with Stage I/II breast cancer, and is preferable because it provides survival equivalent to total mastectomy and axillary node dissection, while preserving the breast.”

Finally, several randomized trials and a summary Meta-Analysis in advanced laryngeal cancer have shown that the larynx and voice can be preserved with XRT + Chemotherapy in the majority of patients with laryngeal cancer without compromising survival [112-113].

Management of localized prostate cancer is a complex subject, even bewildering. Unfortunately, there are no randomized trials to compare surgery vs. radiation therapy. Strong biases exist among both urologists and radiation oncologists. In a 1999 survey of American Urologists, 93% felt that radical prostatectomy was a better treatment than XRT for clinically localized prostate cancer in men with a life expectancy greater than 10 years [114]. In the same survey, 75% of radiation oncologists felt that XRT was equivalent to or better than surgery, and 74% felt that brachytherapy was the same or better than XRT. Due to these biases, it is unlikely that a randomized trial comparing surgery to radiation therapy will ever be completed. The American College of Physicians and Surgeons opened a randomized trial in 2000, with the goal of comparing radical prostatectomy to brachytherapy. The study was closed prematurely in 2004, because only 56 patients out of a planned 1980 had been enrolled [11].

However, there is overwhelming data from the retrospective comparisons reviewed in this article that, multiple comparably good treatment options exist. It is helpful to return to the earlier conclusions reached by the National Cancer Institute and the American Urologic Association. Long-term survival is comparable with either radiation or surgery [8]. Clear-cut superiority of any one treatment currently does not exist [9]. Treatment recommendations should be tailored to the patient’s medical condition, life expectancy independent of the cancer, and aggressiveness of the cancer. Improvements in curative options, such as IMRT, HDR, Cryosurgery, LRP, and RRP continue to evolve. HDR and IMRT compare very favorably to radical surgery and XRT, in regard to cure, morbidity, and quality of life. Fortunately, prostate cancer is rarely an emergent condition. Therefore, patients have time to carefully review the subject, reach a comfort zone, and make the decision which makes the most sense to them.

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