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Multimodal Therapy for Patients with High-Grade, High-Risk Prostate Cancer with Long-Term Follow-up

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Abstract: High risk prostate cancer requires a multimodal approach to treatment. Surgery has played an increasing role for these patients although long-term follow-up and experience with neoadjuvant therapy, a basic tenet of cancer treatment, remains limited. Here we report our experience with neoadjuvant hormonal ablation followed by surgery and postoperative radiation with greater than 20-year follow-up. From 1990-2012, 82 patients with clinically organ-confined prostate cancer and 10 years median follow-up underwent multimodal therapy (MMT) consisting of neoadjuvant hormonal ablation followed by radical retropubic prostatectomy and postoperative radiation. High-risk prostate cancer was defined preoperatively as Gleason Score 8-10 or PSA>20. Patients with negative surgical margins were observed initially and treated with salvage XRT in the instance of recurrence. The MMT protocol was well tolerated in all 82 patients with no treatment-related discontinuation of therapy. Final surgical pathology revealed stage pT3-T4 in 58/82 (71%) and nodal involvement in 7/82 (9%). Distant metastatic disease was identified in 10/82 patients (12%). For patients undergoing MMT at 10, 15 and 20 years, cancer-specific survival was 78/82 (95%), 77 /82 (94%) and 77/82 (94%), overall survival was 68/82 (83%), 66/82 (80%) and 60/82 (73%), and biochemical recurrence was 61/82 (74%), 51/82 (62%) and 35/82 (43%). These findings establish the MMT protocol as an effective treatment strategy for high-risk prostate cancer with excellent long-term cancer-specific survival. Recurrence occurring primarily as a rising PSA as opposed to distant metastatic disease suggests limited morbidity as well among patients treated with this protocol.

Keywords: Prostatic Neoplasms, Neoadjuvant Therapy, Prostatectomy, Radiation

1. Introduction

The management of high-risk prostate cancer remains challenging. Up to 50% of patients experienced recurrent disease following surgery underscoring a great need for better therapies in treating this disease. It is for this reason that we embarked on a new method of treatment for high risk prostate cancer.

Multimodal Therapy (MMT), a concept and term coined by the senior author (J. A. L.) in originating a novel, prospective, non-randomized clinical trial of: neoadjuvant androgen deprivation therapy (ADT), followed by surgery and postoperative radiation, was first used in 1990 to treat the initial patient with high-risk prostate cancer. With a favorable outcome for that patient, ultimately followed for over 20 years with no evidence of recurrence, this introduced MMT as a new treatment paradigm for high-risk prostate cancer. While this protocol was an original concept in 1990, which for years others were reluctant to adopt and even felt was controversial, relatively recently there has been renewed interest in neoadjuvant therapy, particularly given that post-operative recurrence following radical retropubic prostatectomy for high-risk prostate cancer has been associated with prostate cancer-related death in 80-90% of patients [1]. As a result of renewed interest we felt obligated to report our experience with MMT.

In fact, neoadjuvant treatment has become a basic tenet in oncology for multiple tumor types. The reason for this is that neoadjuvant therapy in other tumor types has been shown to be effective in reducing positive surgical margin rates and in achieving improvement in cancer-specific and overall survival. In bladder cancer, for instance, pathologic complete response to neoadjuvant therapy has been correlated with

increased cancer-free survival [2]. And in more recent prostate cancer research, positive surgical margins have been found to correlate with increased biochemical recurrence, with increased utilization of radiation therapy and secondary therapies, as well as (more significantly) increased prostate-specific mortality [3, 4]. Here we examine the efficacy of the MMT protocol consisting of neoadjuvant ADT, followed by radical prostatectomy and post-operative radiation in patients with high-risk prostate cancer with maximum follow-up exceeding 20 years.

2. Methods

From 1990-2012, 82 patients with clinically organ-confined prostate cancer underwent multimodal therapy (MMT) consisting in general of a 3-month course (range 3 – 6 months) neoadjuvant ADT followed by radical retropubic prostatectomy and adjuvant vs. salvage postoperative radiation. High-risk prostate cancer was defined preoperatively as Gleason Score 8-10 or PSA>20. Patients with positive surgical margins received adjuvant XRT. Patients with negative surgical margins were observed initially and treated with salvage XRT in the instance of recurrence. Kaplan-Meier analysis was performed utilizing SPSS statistics software for biochemical recurrence, overall survival, and cancer-specific survival. Adjuvant and salvage XRT CSS were compared. Data was obtained for this institutional review board approved protocol (IRB No. 588815-1) with a median follow-up of 10 years, ranging from 7 months to 21 years (Table 1).

Table 1. *Demographics (n=82 patients).*

Median Follow-up in years	10.1	(7m-21y)
Median age in years	61	(49y-76y)
Median pre-op PSA (ng/ml)	8.4	(.2-107)
Pathologic Gleason sum		
Gleason<8	24 (29%)	
Gleason 8	28 (34%)	
Gleason 9	27 (33%)	
Gleason 10	3 (4%)	
Pathologic Stage		
pT2	24 (29%)	
pT3/4	58 (71%)	
Negative margins	42 (51%)	
Positive margins	40 (49%)	
Lymph node dissection and node status		
Nx	11 (13%)	
N0	64 (78%)	
N1	7 (9%)	
N2	0	
Neoadjuvant ADT	82 (100%)	
Adjuvant Radiation	52 (63%)	
Salvage Radiation	30 (37%)	

3. Results

Patients in this series were found to have high-risk prostate cancer as defined as either having Gleason score 8-10 cancer, a high PSA exceeding 20ng/ml, or advanced stage (pT3/4) disease. Over 40% were diagnosed prior to 2000, indicative of a significant number of patients in the early PSA screening era, and as a result our series is heavily weighted toward palpable, high risk disease. These patients in general have been noted to have more aggressive disease on average. In fact, clinical and pathologic stage migration over the years is a phenomenon which has been described, which is consistent with our experience [5].

This novel MMT algorithm in our experience was well tolerated in all 82 patients with no treatment-related discontinuation of therapy. Final surgical pathology revealed stage pT3-T4 in 58/82 (71%), with nodal involvement in 7/82 (9%). Distant metastatic disease following MMT was ultimately identified in 10/82 patients (12%). Overall survival at 10, 15 and 20 years was 68/82 (83%) and 66/82 (80%) and 60/82 (73%) respectively (Figure 1). Biochemical recurrence was lower at 61/82 (74%) and 51/82 (62%) and 35/82 (43%) at 10, 15 and 20 years respectively (Figure 2).

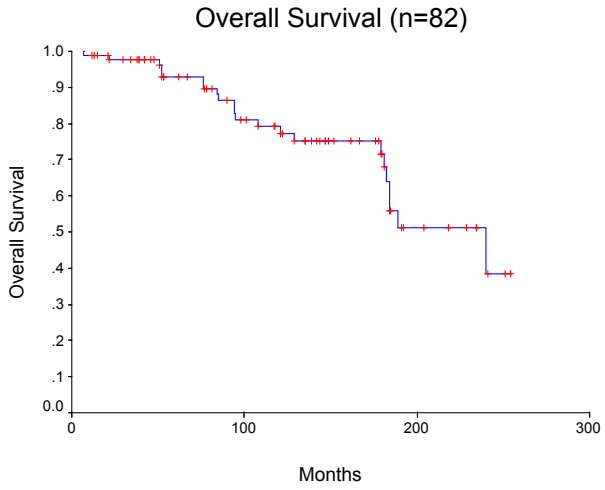

Figure 1. *Overall Survival: Patients with High-Risk Prostate Cancer Undergoing Multimodal Therapy (n=82).*

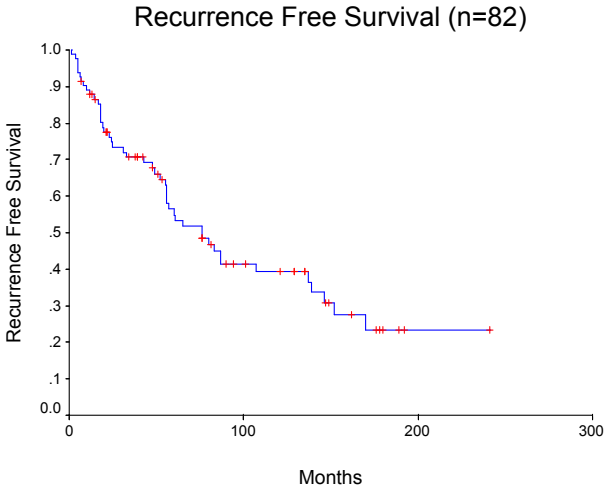

Figure 2. *Freedom from Biochemical Recurrence: Patients with High-Risk Prostate Cancer Undergoing Multimodal Therapy (n=82).*

Cancer-specific survival for patients undergoing MMT at 10, 15 and 20 years was 78/82 (95%), 78/82 (95%) and 77 /82 (94%) and remains unchanged (Figure 3).

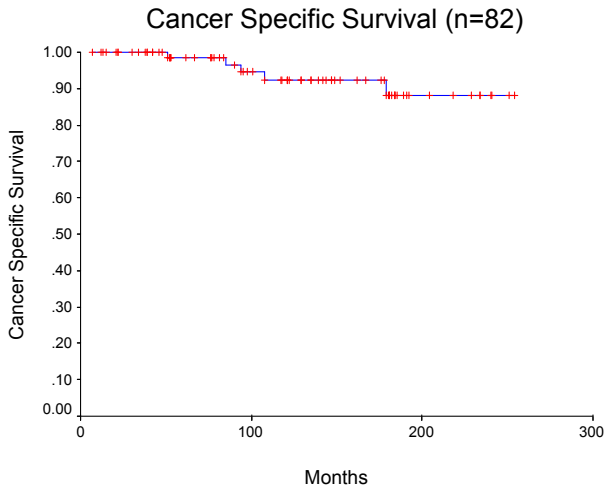

Figure 3. *Cancer-Specific Survival: Patients with High-Risk Prostate Cancer Undergoing Multimodal Therapy (n=82).*

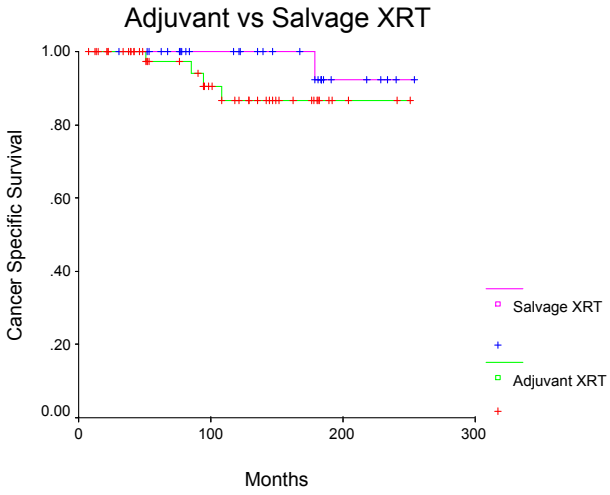

Figure 4. *Adjuvant vs. Salvage XRT: Kaplan-Meier Analysis of Cancer-Specific Survival.*

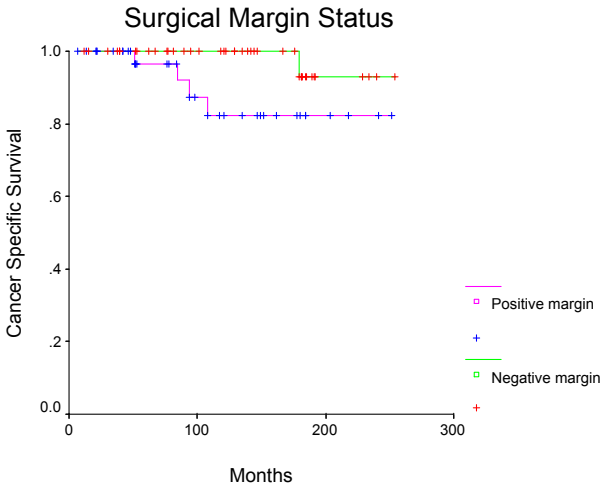

Figure 5. *Cancer-Specific Survival: Positive vs. Negative Surgical Margin Status.*

In subset analyses, we compared patients undergoing adjuvant XRT versus salvage XRT. We found that salvage XRT was effective in this cohort based on cancer-specific survival. More strikingly, patients undergoing salvage XRT appeared to have a better outcome than those undergoing adjuvant XRT (Figure 4). And when evaluating cancer-specific survival on the basis of margin positivity, patients with positive surgical margins fared worse than those with negative surgical margins (Figure 5).

4. Discussion

4.1. Studies of Dual Therapy: Radiation and ADT

We have utilized multimodal therapy in treating patients with high-risk prostate cancer for over 25 years, with the present series of patients dating back to 1990. Acknowledging our initial success with multimodal therapy, radiation oncologists began to explore treatment protocols combining radiation with ADT for patients with high-risk prostate cancer. As a result, multiple studies have established the efficacy of combination (dual) treatment as opposed to single arm therapy of this disease. Short-term ADT in conjunction with radiation was found to improve local control in the RTOG 86-01 [6]. And with long-term ADT in conjunction with radiation in both the RTOG 85-31 and EORTC 22863 randomized clinical trials, a significant improvement in cancer-specific survival was observed with combination therapy [7, 8]. Taking this one step further, the RTOG 92-02 study of short-term (4 months) versus long-term (26 months) androgen deprivation in conjunction with XRT revealed that cancer-related outcomes were significantly improved with long-term treatment. In this randomized trial, cancer specific survival was 90 and 85% at 5 and 10 years respectively [9].

4.2. Studies of Dual Therapy: Surgery and ADT

Given the encouraging initial results of the MMT protocol, combinations of ADT with surgery have also been explored. In contrast to radiation therapy, however, studies exploring combinations of ADT with surgery following the inception of MMT have been relatively limited in scope. Gibbons and colleagues, for instance, describe their experience in treating high-risk prostate cancer with surgery with and without ADT. While a formal protocol was not established in their study, they found that surgery +/- ADT resulted in 5- and 10-year cancer-specific survival of 90 and 80% respectively [10]. In a study of neoadjuvant ADT prior to radical prostatectomy, cancer specific survival was not significantly improved despite a greater likelihood of achieving negative surgical margins [11]. While this study seemingly did not confirm the efficacy of neoadjuvant ADT, there are several criticisms regarding dual therapy studies such as this one. For instance, it has been noted that these studies were underpowered to detect a difference in survival. Secondly, length of follow-up was felt not to be adequate to detect a difference. And thirdly, differences in survival between study arms evaluating neoadjuvant therapy may have been diminished by inclusion of patients in these studies without high risk disease [12].

The reason for this is that definitions of high risk disease can vary [13], and early PSA era cancers presented differently from those of the present era [14], leading to heterogeneous study populations in these studies. While this study combining neoadjuvant ADT with surgery was less promising, this simply underscores the need for a more aggressive multimodal approach for patients with high-risk prostate cancer, with the addition of radiation postoperatively as provided with the MMT protocol.

4.3. MMT Versus Other Therapies: The Importance of Triple Therapy

The combination of neoadjuvant ADT with surgery and postoperative XRT in our experience provided better results than either ADT and XRT or ADT and surgery, underscoring the added efficacy of MMT triple therapy. By incorporating surgery, thereby establishing multimodal treatment of patients with high-risk prostate cancer, we have achieved 94% long-term cancer-specific survival, with long-term median follow-up of 10 years, with maximum follow-up exceeding 20 years. While a formal comparison of clinical outcomes with the MMT protocol versus other treatment regimens would require a randomized trial, our outcomes with MMT utilizing neoadjuvant ADT, surgery and radiation are at least similar if not better than dual-therapy protocols for patients with high-risk prostate cancer. These differences have become more apparent as these patients have been followed over a longer period of time. The reason for the excellent cancer-specific survival with the MMT protocol is perhaps due to the inclusion of all three treatment modalities. While only relatively recently adopted by others in treating high-risk prostate cancer, even in our early experience with the MMT protocol we recognized that surgery does offer important advantages in managing these patients. For instance, surgery also allows for pathologic staging, and therefore more accurate determination of disease, in terms of local extension. Furthermore, surgery also affords the opportunity for pelvic nodal dissection which is crucial in determining prognosis and in treatment planning. In the future surgery, with utilization of modern techniques, can be accomplished with minimal morbidity. In our experience, as has been reported previously, utilization of a bladder neck sparing approach in appropriately selected individuals can result in a 99% continence rate postoperatively. Remarkably, 40 of 200 patients undergoing radical prostatectomy with bladder neck sparing in this series remained fully continent following completion of postoperative radiation [15].

4.4. MMT: The Importance of Therapy Sequence

Another important aspect of the MMT protocol potentially lending to its efficacy is that all three modalities are utilized in the appropriate sequence. For instance, administering ADT in a neoadjuvant fashion allows for downstaging of locally advanced disease. This enables more effective cytoreduction, a basic concept in multimodal cancer treatment in other surgical disciplines, which can provide for more effective local control and treatment of microscopic rather than bulky residual disease. With the MMT protocol, we have found that of patients receiving neoadjuvant ADT who nadir to an undetectable PSA preoperatively, 83% will have negative surgical margins, making us more aggressive surgically and providing better outcomes. Based on our findings as well as those of others, negative surgical margins can translate to less morbidity and better clinical outcomes [3, 4]. And surgery prior to radiation avoids potential toxicity and operative risk due to poor healing of irradiated tissue. Furthermore, findings on surgical pathology can then be used to determine whether radiation should be administered in an adjuvant fashion. In comparing patients undergoing MMT with adjuvant XRT versus salvage XRT, we actually found that patients undergoing salvage XRT had a better cancer-specific survival. However, patients with adverse pathologic features including positive surgical margins and locally advanced (stage pT3-T4) prostate cancer were assigned adjuvant XRT. As such this unexpected result is likely a reflection of patient selection bias with this treatment protocol. It follows that the cancer-specific survival curves stratified for adjuvant versus salvage XRT and positive versus negative surgical margins (Figures 4 & 5) are superimposable, as they are interrelated in this manner in this series.

4.5. Other Advantages of Neoadjuvant ADT

Very recently, approximately 25 years after our initial patient was treated with MMT, there has actually been increased interest in utilizing neoadjuvant ADT prior to radical prostatectomy, in that a group in Boston has recognized its importance, having confirmed our original observations of neoadjuvant treatment and therefore the clinical value of MMT initiated in 1990 [16]. They acknowledge an important clinical advantage of neoadjuvant treatment in that response to treatment can be assessed. This allows for agent selection in these instances, whereby agents inducing response to treatment might be preferred to other ones for subsequent therapy, and agents which are not effective in the neoadjuvant setting might be avoided. In prostate cancer, there is much research regarding molecular and histologic markers of response to ADT. And neoadjuvant approaches to treatment can also be utilized to assess efficacy of novel agents [17, 18].

5. Conclusions

Cure remains the ultimate goal in cancer treatment. However, with high-risk prostate cancer, the risk of biochemical recurrence remains significant, even with the present multimodal treatment strategy. Nevertheless, cancer-specific survival and overall survival remain high with this strategy, and across studies appear to be higher at given intervals of follow-up than conventional treatment with ADT and XRT alone.

A secondary goal of our multimodal approach is to achieve lower local recurrence rates and as such lower disease-related complications. Indeed it appears that the incidence of local recurrence or symptomatic sequelae of cancer recurrence is

relatively low in our series. And now that we utilize MRI for more accurate diagnosis and staging we might expect our outcomes to be even better. For instance, we are now able to diagnose smaller volume cancers with MRI fusion biopsy which are more amenable to surgical removal. Another important difference with contemporary management is that prostate parametric MRI staging preoperatively enables more accurate staging of the local extent of disease, thereby affording better patient selection for surgical removal of the prostate, and better determination of duration of therapy and surgical timing following neoadjuvant treatment to optimize surgical outcomes. For these reasons, with advancing therapies and more sophisticated tools in diagnosing and stratifying prostate cancers, translating to earlier detection and longer lead time lending to longer overall survival with prostate cancer, it appears that the principles of treatment we have established with multimodal therapy will lead to even more successful future treatment strategies for high-risk prostate cancer.

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