

RESEARCH ARTICLE

Treatment for intermediate and high-risk prostate cancer: Controversial issues and the role of hyperthermia

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Abstract

For patients affected by intermediate- and high-risk prostate cancer, a single local therapy is not enough, and a more aggressive treatment, such as androgen suppression therapy (AST) and pelvic irradiation, is indicated. Biochemical disease-free survival (bDFS) and overall survival (OS) improve in intermediate- and high-risk prostate cancer using radiotherapy (RT) combined with AST as compared with the RT alone.

Hyperthermia (HT), combined with RT for the treatment of prostate cancer with intermediate- and high-risk, has been defined as “promising”. In the development of new strategies, the reduction of short and long-term treatment related toxicity is of primary importance. Quality of Life (QoL) has been previously investigated and the authors concluded that HT does not negatively impact QoL in patients treated with radiation and HT. The use of HT in treating advanced prostate cancer has been reported by many centres; several studies suggest the feasibility of HT added to conventional RT.

In intermediate- and high-risk prostate cancer, the combination of RT plus a long-term androgen suppression provides good results in terms of OS and QoL. HT, improving the anti-cancer effects of irradiation, as demonstrated by experimental in vitro and in vivo studies, could increase the outcome in the treatment of locally advanced prostate tumours without adding toxicity. A randomised phase III trial comparing RT-AST combined treatment plus/minus HT is needed to demonstrate the efficacy of HT.

Keywords: High risk, hyperthermia, intermediate risk, prostate cancer

Introduction

In prostate cancer, the traditional prognostic factors are T stage, PSA, and Gleason score (GS). To facilitate treatment recommendations, several risk schemes have been proposed [1, 2]. The risk classification proposed by the Dana Farber Cancer Institute stratifies patients with clinically localised prostate cancer to three risk groups. Low risk is defined as meeting all the criteria: T1c to T2a, PSA ≤ 10 ng/mL and GS ≤ 6 . Intermediate risk is defined as T2b, PSA > 10 but ≤ 20 ng/mL or GS 7. High risk is any of the following: $\geq T2c$, PSA > 20 ng/mL, or GS 8 to 10.

For intermediate- and high-risk patients, a single modality of treatment is likely not enough; a more aggressive treatment, such as AST and pelvic

irradiation, is indicated. HT, associated with RT in locally advanced carcinoma of the prostate, has been defined as a ‘promising modality’ [3].

Hormonal therapy

In 1997 a study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) [4] showed that in patients with locally advanced disease treated with RT alone, the use of goserelin protracted for 3 years could improve both local control and OS for high-risk patients. Long-term results of this study were published in 2002 [5]. An update of this trial (EORTC 22961) has recently been published [6], showing a 5-year overall mortality of 19% for the arm with short-term (6 months) AST and of 15.2% for the arm with

long-term AST (30 months). Similarly, the Radiation Therapy Oncology Group (RTOG) 85-31 trial [7], also published in 1997, showed a significant advantage in terms of local control and disease free survival (DFS) in patients with locally advanced disease treated with goserelin (indefinitely or until progression) starting from the last week of RT, although a significant benefit in OS was evident only in the subgroup of patients with poorly differentiated disease (GS>7) and who did not undergo radical prostatectomy. Long-term results of this trial were published in 2005 [8]. Examining the results of these studies, it appears reasonable to consider an adjuvant AST with LH-RH analogues (lasting more than 2 years) in patients with T3-T4 prostate cancer and unfavourable risk factors, which are candidates for RT.

The RTOG 92-02 trial demonstrated the advantage of adding long-term AST to short-term AST with RT for T2c-T4 prostate cancer [9], with survival advantage in patients with Gleason scores 8 to 10. There are three other phase III trials which showed a survival benefit adding 4-6 months of AST to RT: in the Dana Farber Cancer Institute study, the addition of 6 months of AST to RT resulted in increased overall survival in men with localised but unfavourable-risk prostate cancer [10]; these results may pertain only to men without moderate or severe comorbidity. In the Trans-Tasman study, 6 months' androgen deprivation given before and during RT improved OS in patients with locally advanced prostate cancer [11]. The results of the RTOG 94-08 trial have been presented at the ASTRO meeting in 2009 [12]: 2028 patients (stage T1b-T2b) were randomised to receive either RT alone or 4 months of AST starting from 2 months before RT; estimated OS at 12 years was 51% in the AST-RT arm and 46% in the RT alone arm ($p=0.03$).

The benefit of HT in these trials may be due to the relatively low doses of RT used. As HT has a well-established radiosensitising effect, the use of HT combined with RT and AST may provide further benefit, or, alternatively, HT has the potential to replace AST which is associated with significant morbidities.

Radiotherapy dose-escalation studies

The first positive dose-escalation trial was performed at MDACC [13]: 305 patients (stage T1-T3) were randomised to receive either 70 Gy or 78 Gy of 3D conformal RT; freedom from failure at 6 years was 64% and 70% in the two arms, respectively ($p=0.03$).

A retrospective study from Fox Chase Cancer Center suggests that radiation dose (70 to 72.9 Gy, 73 to 76.9 Gy or ≥ 77 Gy), PSA, clinical T stage, and

GS are significant predictors of biochemical failure, whereas short-term AST and radiation field size are not [14]. In this study, the radiation dose was the most significant determinant of freedom from biochemical failure in patients with a lymph node risk >15%. These data suggested that the primary tumour takes precedence over lymph node coverage or the use of short-term AST. Doses >70 Gy seemed to be of paramount importance in intermediate- and high-risk patients.

Concerning dose-escalation toxicity, the RTOG 94-06, a phase I/II study, showed that dose escalation to 79.2 Gy in 44 fractions of 1.8 Gy/day is well tolerated by men with early-stage prostate cancer and can be delivered safely in the context of a multi-institutional clinical trial; a dose of 78 Gy in 39 fractions of 2 Gy/fraction was associated with a significantly increased rate of moderately severe late toxicity compared to similar doses delivered at 1.8 Gy/fraction [15]. While relatively low, toxicity did increase with dose escalation. A prospective randomised trial (RTOG 0126) was recently completed, to determine whether dose escalation leads to an improvement in overall survival (high dose - 79.2 Gy in 44 fractions - 3D conformal RT/IMRT versus standard dose - 70.2 Gy in 39 fractions - 3D conformal RT/IMRT) in patients affected by localised prostate cancer; the results of this study are not expected for several years.

The Proton Radiation Oncology Group 95-09 study (a randomised trial comparing 70.2 Gy versus 79.2 Gy of combined photon and proton radiation for 393 men with clinically localised prostate cancer (stage T1b-T2b, prostate-specific antigen <15 ng/mL, and no radiographic evidence of metastasis) showed that the estimated 10-year biochemical progression rate for patients receiving standard dose was 32% compared with 17% for patients receiving high dose; after a median follow-up of 9.4 years, treatment with higher dose radiation compared with standard dose was not associated with an increase in toxicity [16].

All these trials demonstrate benefit with dose-escalated RT; as HT has a proven radiosensitising effect, this provides a notable rationale to combine HT with RT.

Pelvic irradiation: yes or no?

The RTOG 9413 study is a landmark trial that consists of a four-arm randomisation scheme to either prostate-only RT (PORT) or whole pelvic RT (WPRT) followed by a prostate boost, and either 4 months of neoadjuvant and concurrent hormones or 4 months of adjuvant hormones [17]. Patients with an estimated nodal risk of >15% or T2c to T4 with a GS of 6 or greater were eligible. The 4-year

progression-free survival was 54.2% and 47% in the combined WPRT arms and PORT arms. When the four arms were analysed separately, the neoadjuvant hormone and WPRT arm (59.6%) had a significantly better 4-year progression-free survival than the other three arms (44.3% to 49.8%). A trend towards increased acute (2% versus 1%) and late (1.7% versus 0.6%) grade 3 to 5 gastrointestinal (GI) morbidity was seen in the combined WPRT and prostate only arms, respectively.

Experimental in vitro studies

Many experimental in vitro studies had preceded clinical experiences by using various heating methods and giving promising results in terms of thermal enhancement when heat was combined with irradiation to treat human prostate cancer cells.

A relevant number of in vitro studies documented the radiosensitising effect of HT and its potential in eliminating hypoxic cells [18]. HT has been reported to be a radiosensitiser in human and rat's prostate carcinoma cells [19–21]. Some studies were performed using two human prostate carcinoma cell lines. The thermal enhancement ratio of a single acute ionising radiation dose following heat delivery ranges from 2.0 to 1.4. Ninety per cent of prostate cancer cells exposed to heat for 24 h were killed, whereas no significant radiosensitisation was found in breast and colon human cells exposed to the same temperature combined with irradiation. However, large differences in extent of thermal radiosensitisation between cell lines are not sufficient to suggest that this effect is particularly high for prostate cancer cells.

The rationale for using HT combined with ionising radiation in prostate cancer seems to be strongly supported by the majority of in vitro studies, with the exception of a study from UCLA, which indicated a risk in heat-related reduction in androgen receptors (AR) level and in an induction of a hormone refractory status in prostate carcinoma cells. However, in the same study the authors confirmed the radiosensitising effects and the cell death induced by heat [22]. In this study, the authors also demonstrated that AR expression was completely abrogated in LnCaP human prostate cancer cells which are AR-positive. The cultures of LnCaP cells lost AR expression after treatment at 44°C for 1 h and the loss of AR expression was dependent on duration of treatment as well as on temperature. The authors also reported that HT causes apoptosis in many cell lines including PC-3 prostate cancer cells and sensitises PC-3 and DU-145 prostate cancer cells to ionising radiation, confirming the role of HT in the treatment of prostate cancer [22]. The mechanisms of progression to hormone-resistant

disease are not yet fully understood, although many hypotheses have been put forward, most of which involve alterations in the AR signalling pathway, but also mutations of the AR gene combined with p53 mutations. The authors concluded that “if the loss of AR in LnCaP cells reflects the behaviour of androgen dependent prostate cancer cells in vivo, our study raises the question as to whether poorly done clinical HT lacking good thermo-dosimetry and insufficient cell killing would drive the rapid acquisition of androgen independency... Further studies are necessary to explore the clinical significance of our findings’ (p. 4842).

In a study from Kyoto University, the nucleotide sequencing analysis of AR gene revealed a single nucleotide substitution within the steroid-binding domain of AR after the temperature was increased from 30° to 41°C [23]. This mutation allowed a moderate thermal instability of androgen binding of patient's receptor. The results of this case report indicate that a point mutation modified the receptor function and caused androgen resistance in this patient. The authors considered this one the mildest form of all androgen insensitivity syndromes ever examined for mutations in the AR gene. These authors demonstrated that an AR mutation depending on a moderate thermal instability might cause androgen resistance. These reports should be accurately considered in order to avoid possible effects of HT in inducing androgen resistance. However, it should be noted that only a cell line showed this effect which appears to be related to both 44°C and a long duration of heating achieved in this in vitro study, values not usually reached in clinical sessions.

No other studies refusing or confirming these data have been reported yet. It should be noted that in the UCLA study [22] the loss of AR expression in LnCaP cells was strongly dependent on both duration and temperature of heat treatment; the duration ranged from 60 to 90 min, respectively. Notably, the temperature achieved was 44°C. Both duration and temperature values were higher than the levels usually reported by other authors usually limited to 30 min at 43°C, more similar to the temperature used in clinical studies. Furthermore, cells growing in tissue cultures seem to be less sensitive to heat than cells growing in animals (nude mice), suggesting that the effects seen in vitro may decrease the potential effects of HT on cells growing as tumour in vivo. Consequently, the conclusion reported by the UCLA group that HT abrogates AR expression in androgen-dependent cells (this promoting malignant progression) should be considered possible only in case of cells growing in tissue culture, being the behaviour of androgen-dependent prostate cancer in vivo not yet experienced.

Compared with the great number of positive effects of HT in controlling prostate cancer cells, this report could not be considered sufficient to put aside the advantages offered by heat-radiation combined treatment in prostate cancer cells.

In conclusion, the complexity of interactions between ionising radiation and heat appears to increase when we also consider AR level modification and its possible effects on AST. The effects of radiation and HT are synergistic, and this combined treatment might be an important tool in achieving a better tumour control. The temperature achieved, the technique and the exposure time may have an important role on tumour cell death when HT is proposed in clinical trials. Further investigation is needed in order to better understand the various mechanisms of a combined treatment regimen in killing prostate cancer cells.

The rationale for using hyperthermia in prostate cancer

Both bDFS and OS improve in intermediate- and high-risk prostate cancer using RT combined with AST as compared with the use of RT alone or deferred AST until relapse [24]. Considering that long-term AST may increase the risk of fatal myocardial infarction, induce a metabolic syndrome with possible fractures and reduce QoL, some authors [10] thought that a short term AST (no more than 6 months) could be preferable in order to decrease side effects. Nevertheless, the EORTC protocol 22961 [6], comparing RT plus AST for six months followed by no further suppression (short-term group) versus AST for 2.5 years (long-term group) demonstrated (in the high-risk patient population) better results in terms of OS and no-change in QoL in the long-term group, as compared with the short-term group. In the development of new strategies, the reduction of short and long-term treatment-related toxicity is of primary importance. Toxicity profile and QoL are usually secondary but important endpoints in evaluating the efficacy of HT. HT combined with RT in the treatment of locally advanced prostate cancer was associated with a favourable toxicity profile in a phase II study at the Dana-Farber Cancer Institute including men affected by prostate cancer with clinical

stage T2b-T3b, treated with a trans-rectal ultrasound (TRUS) HT system [24]. The protocol also included an AST regimen consisting of LHRH agonist with a non-steroidal anti-androgen for 6 months, inclusive of 2 months of neo-adjuvant AST before initiating RT. In the 35 patients who received two HT treatments, no acute and late grade ≥ 3 toxicity occurred. The rate of acute grade 2 proctitis was greater for patients with a rectal temperature $>40^{\circ}\text{C}$. The increase in acute rectal toxicity with allowed rectal temperatures $>40^{\circ}\text{C}$ did not translate into increased late rectal toxicity. Median time to occurrence of late toxicity was 13 months. The authors concluded that TRUS HT combined with RT for the treatment of locally advanced prostate cancer is safe and well tolerated.

Also, QoL has been previously investigated and authors concluded that HT does not seem to decrease QoL in patients treated with additional HT [25]. The use of HT in treating advanced prostate cancer has been reported by many centres and several studies suggest an improvement in outcome when HT is added to conventional RT.

In 1991, authors from Stanford University reported encouraging results using external-beam RT plus HT in patients affected by prostate cancer recurrence previously treated with brachytherapy, achieving a clinical complete response in 75% of patients [26]. Also, at Northwestern University in Chicago, pre-irradiated patients were re-treated with HT combined with irradiation; all patients reached a complete response by 2–6 months after treatment [27].

Treatment recommendations

A summary of recommendations of how to treat intermediate- and high-risk prostate cancer is given in Table I. HT seems to have a potential benefit in patients with intermediate-risk disease, in which group the data showing a benefit for short-term AST all used low doses of RT. For high-risk patients, the evidence of a real efficacy of HT is less strong, especially given the poor results for very advanced disease.

Table I. Treatment recommendations for intermediate- and high-risk prostate cancer.

	Favourable intermediate risk	Unfavourable intermediate risk	High risk
RT	PORT (70–76 Gy)	WPRT (45–50.4 Gy) + boost (up to 74–78 Gy)	WPRT (45–50.4 Gy) + boost (up to 74–78 Gy)
AST	Neoadjuvant (2 months) Concurrent	Neoadjuvant (2 months) Concurrent \pm adjuvant	Neoadjuvant (2 months) Concurrent \pm adjuvant (24–36 months)
HT	Indicated	Indicated	Not so indicated

Methods

Many methods can be used for prostate HT; the following chapter is a summary of techniques used in previous clinical trials.

Regional hyperthermia

Regional HT is performed with a phase-array applicator with multiple antennas (to a total of 24 antennas allocated in eight dipoles in three rings such as in the BSD 2000 Sigma Eye equipment). Usually, the HT system operates at a frequency of about 100 Hz. A water bolus, filled with a supply tube which maintains a continuous cooling flux during the treatment, couples the radio waves to the patient. During HT, the patient is positioned into the ring applicator with the filled water bolus around his body having a water pressure of about 100 mm; a treatment lasting about 60–75 min is usually well tolerated; it can be shortened in case of back pain or general discomfort. The pressure of the bolus above the patient of a water column of about 100 mm, is usually well tolerated. The treatment can last up to 75 min; treatment reductions can be made in case of back pain or general discomfort. Generally, 1 or 2 treatments per week are performed, for a total of 5 to 6 sessions. Temperatures in the prostate can be measured invasively by placing a central and a peripheral catheter transperineally. Non-invasive thermometry (i.e. placing a catheter in the rectum, urethra and bladder) can be performed as well, although intraluminal thermometry cannot reliably predict the invasive temperatures. These catheters allow introduction of high-resistance thermistors of 1.1 mm diameter with a stepping motor system to monitor the temperature along each catheter track.

Interstitial hyperthermia

Interstitial HT can be performed with an array of electrodes implanted into the prostate with a perineal approach utilising a special template. Each needle is electrically insulated from normal tissues. One to three additional plastic catheters can be implanted for automated temperature mapping. The procedure is performed transperineally under ultrasound guidance and can be an adjuvant to interstitial ^{192}Ir brachytherapy. A temperature goal of 43°C for 45 min can be achieved, immediately prior to the insertion and immediately following the removal of the ^{192}Ir . The catheters can also be placed in the prostate through a template, under TRUS guidance. The number of catheters can be 7 to 16. A probe containing two electrodes is inserted and thermometry used within the probes for online temperature control. A reconstruction of the implant can be done using ultrasonography.

Another way of performing interstitial HT can consist of implanting self-regulating ferro-magnetic thermoseeds, which generate heat by induction in a magnetic field. Paramagnetism occurs when the temperature of the alloy increases above a certain level. If ferro-magnetic material is exposed to a surrounding field, atomic dipoles straighten out and, when the field oscillates, heat is generated. The material heats up until the Curie temperature is reached and the ferro-magnetic characteristics are lost. The selection of alloys with a known Curie temperature allows for a self-regulating system. Based on these specifications, thermoseeds with a higher Curie point can be chosen (i.e. 55°C), which allows for application of temperatures required for HT or thermoablation as well. Treatments usually last about 60 min.

Transrectal ultrasound hyperthermia

The ultrasound power is delivered from a water-cooled 16-element partial-cylindrical intracavitary array. Power deposition is individually controlled for each of the 16 transducers, and a closed heating/cooling system using degassed bolus water is used to control the anterior rectal wall temperature. The cooling water bolus is continuously circulated under a latex membrane secured over the ultrasound probe, which is inflated with the water once inserted in the rectum, to provide coupling to the rectal wall for optimal transmission of ultrasound to the prostate. Between this first and a second latex membrane, three thermocouple sensors spaced 10 mm apart are positioned against the anterior rectal wall. Three interstitial temperature probes with seven thermocouple sensors per probe are used to monitor intraprostatic temperatures, and a single perfusion probe is placed intraprostatically, so that blood flow within the prostate can be recorded before and after HT.

Patients are placed in the lateral decubitus position for treatment. Placement of the interstitial temperature and perfusion probes is accomplished via a transperineal route using transrectal ultrasound guidance. Once the probes are satisfactorily placed within the prostate, the transrectal HT probe is introduced into the rectum.

Power is then applied for a minimum goal of 60 min at therapeutic temperature; this is defined by attainment of 42°C by at least one intraprostatic temperature sensor or allowing for 10 min of initial heating. The thermal treatment goal is to achieve a cumulative equivalent minutes (CEM) T90 43°C of 10 min. This parameter is used to equate a range of actual temperatures achieved with a reference temperature (43°C).

The temperature exceeded by 90% of the measured temperature points (T90) when given over

a period of time is converted to equivalent minutes at 43°C as defined by some authors [28]. The CEM T90 43°C is the summation of the equivalent minutes T90 43°C for each HT session over the course of treatment.

Results

Efficacy

In prostate cancer treatment, the results obtained by using innovative therapies are usually evaluated in terms of bDFS, even if the reduction in prostate cancer-specific mortality remains the most pertinent method to measure the effectiveness of treatment. AST probably does not reduce distant failure directly but rather improves local control as demonstrated in a study from MSKCC, in which the local control was associated with a decrease in distant metastases and prostate cancer mortality [29].

Authors adding HT to irradiation achieved contradictory results in terms of bDFS (Table II). Biochemical failure has been reported differently over time; for each of the following studies, we will mention the criteria used for defining bDFS.

In the study from the Utrecht group, the authors, examining 26 patients affected by T3-T4 prostate cancer treated with regional and interstitial HT, reported a bDFS value of 70% at 36 months, obtaining better results with regional rather than with interstitial HT (79 versus 57%) [25]; an increase in the PSA on two consecutive measurements was considered a biochemical relapse; however, these good results should be confirmed by a longer follow up.

The study from Duke University evaluated 21 patients, 18 affected by primary cancer (89% with T3-T4 tumours, 61% with GS of 7 to 9 and mean pre-treatment PSA of 69 ng/mL), and 3 recurrences and reported a bDFS rate of 25% at 36 months; an increase in the PSA of $\geq 10\%$ on two consecutive determinations was considered a relapse; the authors used RT doses in the range of 65–70 Gy without adding AST [3].

The group from Berlin treated 22 patients, 15 with stage T3pN0M0 and 7 with recurrence. The mean RT dose was 68.4 Gy and only five of them received a short course of AST. The group with primary tumours obtained a 6-year bDFS more than 50% [30]. PSA progression was defined for cases exceeding 2 ng/mL; PSA levels between 1–2 ng/mL were also deemed to be a progression, if PSA increased at two successive controls; local progression was defined as macroscopic tumour growth of $>25\%$.

In a study from the University of Arizona, 26 patients staged C2-D1 (AUS classification) with a median pre-treatment PSA value of 29 ng/mL were

treated [31]; the study reports the long-term follow-up of a previous trial from the same centre [32]. The authors delivered a mean RT dose of 68 Gy and used a TRUS HT method; they obtained a 5-year bDFS of 35% without adding AST. Biochemical failure was defined according to ASTRO criteria [33] as three consecutive increases in PSA.

Recently, the results of the DFCI 94-153 phase II trial of TRUS HT in combination with radiation and AST have been presented at the annual meeting of the Society for Thermal Medicine in 2010 [34]. Thirty-seven patients with clinical T2b-T3b prostate cancer received approximately 70-Gy RT plus two TRUS HT treatments; subsequent to the first four patients, 6 months of AST was allowed (LHRH agonist with a non-steroidal anti-androgen, including 2 months of neo-adjuvant AST before initiating RT. Median follow-up was 70 months (18–110 months). The absolute rate of bDFS at 2 years was improved (84%) when compared to the bDFS rate (64%) in the similar arm of the RTOG 92-02 trial (RT plus 4-month AST without HT) [9].

In our institution's experience, the addition of regional HT to radiation in patients with locally advanced stage (T2b-T4N1) reached a 5-year bDFS of 49% [35]; we defined biochemical failure according to ASTRO criteria [33]. Our results are similar to the ones of the RTOG study 94-13, which reported a 4-year DFS rate of 44.3–49.8% in patients with similar stage (estimated nodal risk $>15\%$, T2c-T4, GS ≥ 6) [17]; in this trial, an event for biochemical failure was defined as two consecutive and significant PSA rises separated by at least 1 month. Only the arm treated with neoadjuvant AST and whole pelvic RT followed by a prostate boost had a better 4-year DFS (59.6%). Considering the different follow-up (4- versus 5-year survival of our study) and the different AST administration modality (4 months of adjuvant and concurrent hormones in all patients of RTOG study versus 6 months only in 52% of our patients), our results could be considered promising.

Interstitial HT was used in the series published by the group from Stanford University [36] and by the group from Berlin [37]. The former associated interstitial HT with ^{192}Ir interstitial brachytherapy, demonstrating that the procedure is feasible and well tolerated. In the latter study, ferromagnetic thermoseeds were implanted in the patients; the combined external RT-interstitial HT system resulted in a steep decrease of the median PSA value; looking to the PSA response, the authors achieved a similar decrease in PSA to the HDR brachytherapy cohort [38]; they concluded that it is possible to deliver a high biologically effective dose of radiation in the form of effective interstitial HT combined with 3D conformal RT. They also achieved intraprostatic

Table II. Main characteristics of published clinical trials performing HT in prostate cancer.

Type of hyperthermia	Author	Number of patients	Stage	Radiotherapy dose (Gy)	Hormal therapy	bDFS	OS	Toxicity
Regional HT	Anscher (1997)	30	T3,4	65-70	No	At 3 years: 25%	At 6 years: 60%-95%	20 cases grade 2-3
	Tilly (2005)	22	cT3 pN0 or recurrent T2b,4 N0,1	68,4	5/22 patients		At 5 years: 87%	1 case grade 3
Interstitial HT	Maluta (2007)	144	T2b,4 N0,1	70-76	125 patients	At 5 years: 49%		No more than grade 2
	Prionas (1994) Deger (2004)	36 57	B,C T1,3	(192 Ir-brachytherapy) 68,4	No No	At 40 months: 65%-95%		4 cases grade 3
Regional or interstitial HT TRUS HT	Van Vulpen (2004)	Regional HT 14; interstitial HT 12	T3,4 NX/0	66-70	No	At 3 years: 70%		No more than grade 2
	Algan (2000)	26	C2,D1	50-68	No	At 5 years: 35%	At 5 years: 70%	1 case grade 3
	Hurwitz (2005)	37	T2b,3b	66,6	33 Patients			No more than grade 2

temperatures of up to 48°C while the temperatures in the rectum and urethra were moderate.

In all these series, bDFS did not reach the remarkable results of other series with RT and prolonged AST without HT, such as the one from Hanover (86% at 5 years, 74% at 7 years) [39]; biochemical relapse after irradiation was defined as a PSA of 0.4 ng/mL or more and three consecutive elevations of serum PSA. Commenting on the results of the RTOG 85-31 trial [7, 8] (which demonstrated that maximum androgen blockage prior to and during RT increased local control and bDFS compared to radiation alone), these authors pointed out that the short-term androgen ablation did not significantly enhance local control or survival in high-risk patients, but only in intermediate-risk ones. Long-term androgen suppression in high-risk prostate cancer is probably related to a longer bDFS; conversely, in most series performing HT, AST was used in a subset of patients or in no patients at all, and this may explain the difference in terms of bDFS.

Reviewing these studies, we may conclude that low doses of RT and lack of AST administration in the majority of patients treated using HT are responsible for the lower bDFS rate. Indeed, bDFS more than OS depends on the addition of AST as demonstrated by five randomised studies [5, 8, 40–42]. The addition of HT to RT can be done safely, but its value for disease control is uncertain at this time.

Comparing the data from various trials, the DFS ranges from 21% to 67% using RT alone and by 36% to 89% adding AST to RT. Considering that in these studies similar doses of RT (range 64–70 Gy) were delivered in both arms, the better result obtained in the experimental arms has to be attributed only to AST. Recently, using some technical improvements such as intensity modulated radiation therapy (IMRT), the maximum tolerated dose may reach 75–80 Gy, without increasing the dose-related toxicity.

Combining HT with higher doses of radiation (74–76 Gy) than in the previous randomised studies and short term AST in patients at high risk of local and distant metastases could be a promising method to achieve better results in terms of bDFS and OS, without increasing AST side effects. We would recall the sentence of D'Amico: 'Given the growing list of toxicities of AST, some of which can shorten life especially in advanced-age men, administering as little AST as possible while maintaining the approximately 100% reduction in all-cause mortality is our current challenge' [43].

Quality of life

QoL, defined as an individual perception of well being, affecting physical, social and emotional

functions in the cultural and social context, has been evaluated in many published series. In general, men who underwent radical surgery or RT reported poorer sexual function than those without prostate cancer, but there were no statistical differences in sexual and bother functions between patients with surgery intervention and patients treated with RT. Sexual, urinary and bowel aspects remained stable from two to seven years after radical prostatectomy, however general health appeared to significantly deteriorate regardless of the patient's age and the time they are given the questionnaire [44]. The addition of RT to radical prostatectomy versus radical prostatectomy alone increased both urinary and bowel dysfunction, but the bowel dysfunction disappeared over the 5-year period. The addition of RT did not negatively impact the erectile function [45].

A recent investigation suggested that sexual function does not have a continuous decline after irradiation; instead, it decreases maximally within the first 24 months after the treatment, with no significant changes thereafter [46].

The EORTC is conducting many clinical trials assessing QoL in various diseases and it validated a specific questionnaire on the prostate (PR 25) in addition to the generic QLQ-C30.

Using the PR 25 and the QLQ-C30 questionnaires, the group from Utrecht, in patients treated with HT and ionising radiations, did not demonstrate any statistically significant difference in QoL between patients receiving regional or interstitial HT plus RT and the group receiving irradiation alone [47].

In our institution we performed a QoL survey in the series of patients previously cited [35]. After 2–7 years from the end of RT, 107 patients out of the 144 patients of the series were asked to be evaluated with the UCLA-PCI questionnaire which tests urinary, bowel and sexual function and bother; only 74 patients agreed. The results revealed good QoL levels, except for sexual function, although the patients did not feel sexual decline as a big problem (sexual bother scores were relatively high). All scores were comparable to those of an Italian series with radical prostatectomy [48].

Conclusion

In intermediate- and high-risk prostate cancer, the combination of RT plus AST provides good results in terms of OS and QoL. WPRT seems to yield a better outcome than PORT but this issue is still a matter of debate; some high-risk patients may benefit from it, but this remains controversial.

HT (either performed as regional, interstitial, or TRUS HT) has the potential to improve the anti-cancer effects of irradiation, as demonstrated by

experimental in vitro and in vivo studies. Completed clinical trials have shown promising results with the addition of HT to RT and AST. Phase III trials assessing the addition of HT to RT, and when clinically indicated AST as well, are warranted.

QoL studies are increasingly performed for prostate cancer patients to test the impact of various treatments. In our cohort of patients, the addition of HT to RT and AST did not have a negative impact on QoL.

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