Prostate cancer radiotherapy 2002: the way forward

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In November 2000, the GU Radiation Oncologists of Canada had their first meeting, "Controversies in prostate cancer radiotherapy: consensus development". The success of this meeting prompted a second meeting, held in December 2002 to discuss "The Way Forward" in prostate radiotherapy. Radiation oncologists from across Canada were brought together and integrated with key opinion leaders in prostate cancer treatment from throughout North America. The group debated current controversies including: intensity modulated radiotherapy (IMRT), external beam hypofractionation, high dose-rate brachytherapy, and hormone therapy in the management of prostate cancer. The meeting also sought to identify and prioritize clinical trial opportunities and to highlight steps required to achieve these research goals.

In summary, advances involving IMRT have enabled the use of higher radiation doses without increasing morbidity. With renewed interest in hypofractionated radiation schedules, the value of hypofractionation using IMRT was discussed and initial results from ongoing clinical trials were presented. The emerging role for high dose-rate brachytherapy in higher risk patients was also discussed. Based on existing preliminary evidence the group expressed enthusiasm for further investigation of the role for brachytherapy in intermediate to high-risk patients. Despite significant advances in radiotherapy, hormone therapy continues to play an important role in prostate cancer treatment for patients with intermediate and high-risk disease. Although evidence supports the effectiveness of hormone therapy, the optimal timing, and duration of hormonal treatment are unclear. Results from ongoing clinical trials will provide insight into these questions and will assist in the design of future clinical trials.

Key Words: prostate cancer, IMRT, hypofractionation, brachytherapy, hormone therapy, clinical trials

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Introduction

On December 5-7, 2002 the Canadian GU Radiation Oncologists met in Montreal, Quebec to discuss "The Way Forward" in prostate cancer radiotherapy. This meeting was planned following a successful first meeting (November, 2000), which set out to develop consensus on a risk stratification model for localized prostate cancer.[1] The first meeting also focused on developing consensus on the role of conformal radiotherapy, brachytherapy and hormonal therapy with radiation in men with non-metastatic prostate

cancer.[1] The goal of the second meeting was to bring together radiation oncologists from across Canada to discuss and debate current controversies in prostate cancer therapy and to identify clinical trial opportunities in radiation oncology. The faculty included some of North America's most respected opinion leaders in prostate cancer treatment (Drs. Jack Fowler, Patrick Kupelian, and Michael Zelefsky), and Canadian radiation oncologists. The meeting held multiple presentations, workshops and discussion sessions with the aim of providing a forum of sharing knowledge and experience between colleagues and peers.

The discussion focused on a few key areas:

- Intensity modulated radiotherapy (IMRT)
- Hypofractionation
- High-dose rate brachytherapy
- Hormone therapy

Advances in conformal radiotherapy, including IMRT, have enhanced the treatment capabilities of radiation for prostate cancer. Coupled with an interest in hypofractionated radiation schedules, significant discussion was generated regarding the current experience with these radiation schedules and the potential of hypofractionation regimens using IMRT techniques. Further, high dose-rate brachytherapy in combination with external beam radiation is a newer technique that has the potential to deliver higher radiotherapy doses to the prostate. The status of high dose rate brachytherapy was discussed during the meeting and enthusiasm was shown for clinical trials involving HDR for intermediate to high-risk patients. Despite these advances in radiotherapy, hormone therapy continues to play an important role in the treatment of prostate cancer. However, clarification of optimal timing, duration and patient population is necessary. Clinical trial opportunities involving hormone therapy were discussed, as were many other trials related to improving radiation therapy for prostate cancer.

This paper highlights the treatment issues discussed at the 2002 GU Radiation Oncology meeting and presents a summary of the ideas and perspectives generated by the group in the hope that it will pave *The Way Forward* in the management of prostate cancer.

Intensity modulated radiation therapy

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Background

Intensity modulated radiation therapy (IMRT) is a technique for delivering external beam therapy to highly conformed treatment volumes by means of segmenting each beam into hundreds of beamlets, each of which has its radiation intensity under individual control. The intersection through a treatment volume of several to many modulated radiation beams provides the possibility of an almost infinite number of combinations and permutations of beamlet number, direction and radiation intensity. The resultant dose distributions have the properties of a very sharp dose fall off beyond the intended high-dose volume, and the ability to "sculpt" the high dose volume into irregular three-dimensional shapes. These volumes can be constructed to follow the contours of irregularly shaped tumors, and to avoid excessive irradiation to uninvolved critical adjacent structures Figure 1.

Disadvantages of IMRT compared to conventional radiation includes the delivery of a higher integral dose, or the irradiation of a greater volume of normal tissue to a low radiation dose that with conventional radiation, and a less homogenous radiation dose delivered to the high dose volume. The former has potential but currently unknown implications for increasing the risk of radiation induced malignancies, and may be a more important consideration for young patients who receive IMRT. The latter feature is mainly important in that radiation planners must be alert to the possibility of unwanted radiation "hot-spots" appearing in critical structures, and once these are identified, radiation plans can generally be modified to minimize hot spots or to move them to less critical areas.

IMRT treatment planning

IMRT plans are usually generated with a planning technique known as inverse treatment planning. With conventional "forward" treatment planning, a treatment volume is identified by an oncologist on cross sectional imaging and a planner then goes through a series of iterations to modify a standard treatment plan to optimize radiation coverage of the treatment volume and to minimize dose to the identified critical structures.

In inverse planning, the treatment volume and the volumes that contain critical structures are identified to the planning system, along with the desired or acceptable radiation doses to each of these volumes. The inverse planning system will go through thousands of iterations to combine beamlet number, direction and intensity to achieve a treatment plan to meet the dose constraints that were originally provided.

Each IMRT treatment plan is very complex and unique, and before treatment is delivered the computer generated model must be verified by actual radiation measurements in radiation phantoms.

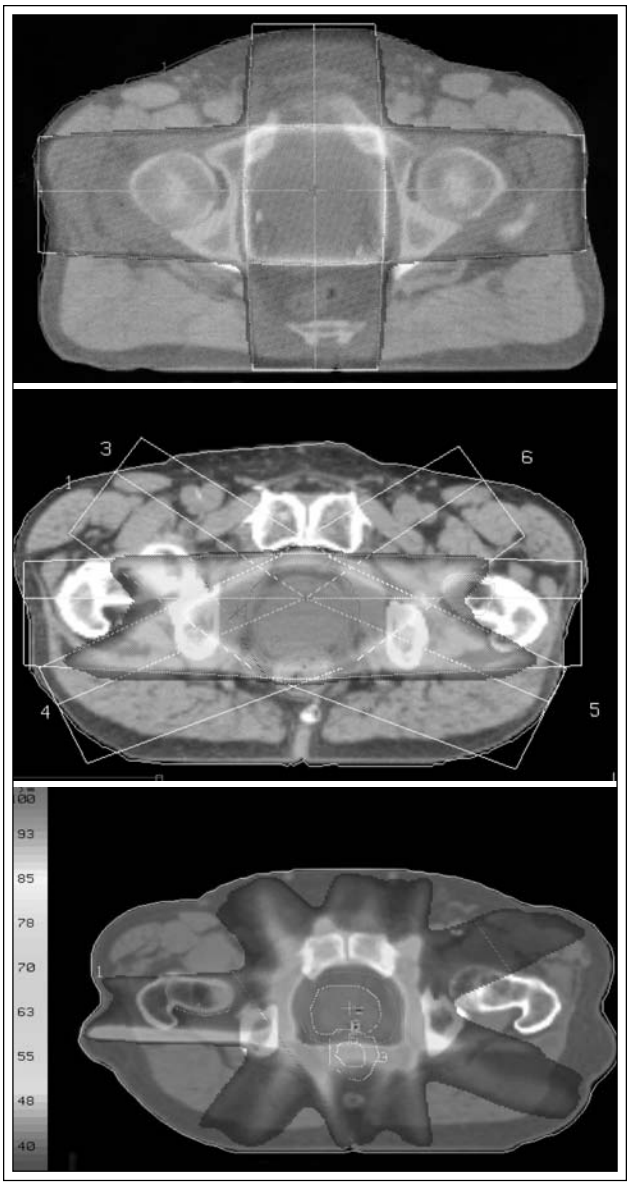

Figure 1. Radiation treatment techniques for localized prostate cancer. Radiation isodose areas are shown on planning CT scan slices. The central area on each image represents the region of highest radiation dose. The IMRT technique demonstrates the smallest and most conformed high-dose radiation volume about the prostate.

This quality assurance process is labor intensive, and is a necessary step until sufficient clinical experience with IMRT provides assurances that the computer models are accurate in a wide range of clinical scenarios, or until acceptable and useful class solutions for IMRT treatment planning are developed. Prostate cancer patients have more consistency in the size and shape of the treatment volumes and the adjacent critical structures than do other tumor sites, and it is likely that IMRT planning workload requirements will be reduced once acceptable class solutions are developed for at least some prostate patients.

IMRT treatment delivery

The potential of IMRT to provide very precise radiation delivery will be fully exploited only if similar accuracy is applied to treatment volume identification and to minimizing random and systematic errors that occur during treatment planning and set-up, including prostate motion caused by changes in rectal and bladder filling. Inter-observer variation in prostate contour delineation has been shown in one study to be reduced by planning on fused MRI images[2].

Random set-up errors may be reduced with patient immobilization, but the type of immobilization used and whether patients are positioned supine or prone will have an impact on treatment cost, therapist convenience and time, patient comfort and the amount of prostate motion observed. A recent study by Bayley et al randomized patients undergoing 3D conformal prostate radiotherapy to be immobilized supine in a Vac-Loc™ device and prone in a Hip-Fix™ device.[3] Supine immobilization was found to be significantly superior to prone in terms of overall cost, therapist convenience, and patient comfort. Furthermore, supine patients could be planned with a smaller margin for the planning target volume because of smaller prostate motion detected in this group.

Prostate motion due to daily changes in bladder and rectal filling remains the most significant source of inter-fraction set-up error, and variation in target organ position of as much as 15 mm was identified in one study.[4] This source of treatment error must be corrected for by measurement in population studies and included in the planning target volume,[5] or measured and corrected for each patient on a daily basis,[4,6] or minimized by teaching patients to control bladder and rectal filling,[4] or by immobilizing the prostate with an inflatable rectal balloon.[7] The smallest planning target volume margin that accounts for motion error will have the greatest impact on potential bladder and rectal sparing, and this will be best achieved by identifying and correcting for daily prostate motion, or by minimizing prostate motion.

The possibility of minimizing prostate motion and day-to-day variability by educating patients on ways to self-regulate bladder and rectal filling is currently the subject of a prospective study at the Princess Margaret Hospital. Inflatable rectal balloons are effective organ immobilization devices, but they are limited by being inconvenient, intrusive, and uncomfortable.

Daily on-line imaging of prostate position has the advantage of correcting for random and systematic setup errors as well as for organ motion. Prostate position may be assessed on-line by imaging implanted fiducial markers with an amorphous silicone imager, or with an on-line ultrasound imager. Marker implantation is invasive, but marker imaging and image matching has the advantage of being less user dependent and patient dependent than ultrasound localization.[8] Whatever steps individual centres take to minimize planning and setup errors when implementing IMRT, it is important that each centre be aware of the errors inherent in their own techniques and to account for these in their chosen margin for the planning target volume.

Application of IMRT to prostate cancer radiotherapy

The initial clinical application of IMRT for localized prostate cancer was to use the improved bladder and rectal sparing characteristics of the technique to reduce the toxicity of dose escalated conventional 3D conformal radiotherapy (3D-CRT) Figure 2.

Zelefsky et al have shown that for 772 patients treated with IMRT, the combined acute grade 1 and 2 rectal toxicity and late grade 2 rectal bleeding were significantly lower in patients treated to 8100 cGy with IMRT compared to 3D-CRT.[9] Actuarial 2-year rectal bleeding rates were 10% for 3D-CRT and 1.5% for IMRT.

An alternate and innovative use for IMRT in the treatment of localized prostate cancer is in the development of hypofractionation treatment regimens. Recent radiobiological evidence strongly supports the hypothesis that the ab ratio for prostate cancer is low and in the region of 1.2-1.5 Gy.[10,11] If this is the case, then dose escalation regimens biologically equivalent to conventional courses of 8 weeks or longer could be given over a much shorter time using large dose per fraction radiation. This would be of economic benefit, as well as an improvement in patient convenience. The increased risk of late complications from large dose per fraction irradiation could be minimized by employing the improved tissue-sparing characteristics of IMRT.

Kupelian et al reported on 166 patients with localized prostate cancer treated with an IMRT hypofractionation regimen of 2.5 Gy per fraction to a dose of 7000 cGy, with daily ultrasound prostate localization.[12] Actuarial 30-month grade 2 and 3 rectal toxicity was 5% and biochemical relapse-free survival was similar to a contemporary cohort treated to 7800 cGy with conventional fractionation and 3D-CRT.

Catton et al reported on 61 patients with localized prostate cancer treated with an IMRT hypofractionation regimen of 3.0 Gy per fraction to a dose of 6000 cGy, with daily prostate localization using implanted fiducial markers, and followed for a maximum of 22 months.[13] Acute grade 3 toxicity was limited to one patient with grade 3 rectal toxicity. No late grade 3 toxicity was observed, and only one patient with late grade 2 bladder toxicity has been observed in 33 patients followed between 6-22 months.

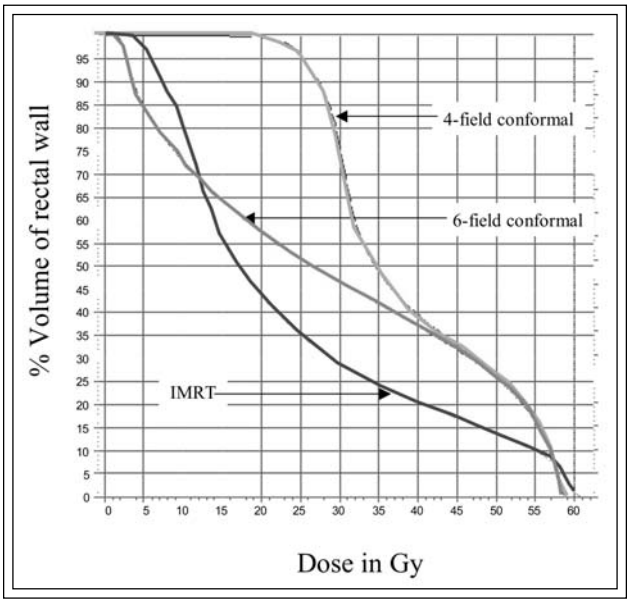

Figure 2. Rectal dose-volume histograms for conformal radiation treatment plans using 4-field, 6-field and IMRT techniques. The margin about the prostate is the same for all three techniques (dose 60 Gy in 20 fractions). The maximum dose received by the percentage volume of rectal wall is shown in Gy. IMRT shows superior rectal sparing at all dose levels between 12 and 58 Gy.

Additional follow-up is required to determine the efficacy of these hypofractionation regimens, and eventually they will need to be tested in randomized trials against conventional dose escalation. The preliminary evidence supports the contention that escalated dose hypofractionated regimens can be given safely using IMRT techniques.

Summary

The high precision of IMRT requires that every centre intending to implement this technique evaluate their own sources of error, and incorporate them into an appropriate margin for the planning target volume. The superior tissue avoidance characteristics of IMRT enhance the ability to safely administer very high doses of radiation to the prostate with conventional fractionation. It also opens the way to the

investigation of alternate fractionation schedules, and preliminary data supports the safety of dose-escalated hypofractionation of prostate cancer with IMRT. The next step is to investigate the efficacy of hypofractionation in a national randomized trial.

High dose rate brachytherapy

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Over the last decade, brachytherapy using permanent seed implants has emerged as a treatment option for many men with low risk prostate cancer, and is currently available in 12 centres across Canada. High dose-rate brachytherapy (HDR) is another form of brachytherapy in which temporary catheters are placed into the prostate and treatment delivered with a high activity iridium source which sequentially steps through the catheters. The radiation dose distribution is precisely controlled by varying the length of time the source stops at each position along the catheters. It allows for better dose coverage of the target, consistent dose coverage outside the gland, and better control of dose to the urethra, bladder and rectum. Large radiation doses are delivered in minutes rather than months, which result in different radiobiological effects to that of low dose-rate permanent seeds. Radiation delivered in this manner would be expected to inflict greater damage to late responding normal tissues or certain cancers particularly sensitive to large radiation fraction size. It has been used extensively to treat cancers in other tumor sites. Recent evidence that prostate cancer is more sensitive to large fraction size[10] has led to greater interest in exploring HDR for this disease. Unlike permanent seed implants, HDR is almost always combined with external beam radiotherapy and is typically administered in more than one fraction with resultant greater workload and less patient convenience. It is currently available in six Canadian centres.

As yet, there is limited data on its clinical efficacy and long-term toxicity. It is tolerated well acutely, with a low incidence of acute urinary and rectal toxicity. Only nine centres in Europe and North America have reported their experience, with a wide range of dose and fractionation being used, and also variability in implant technique Table 1. Only six of these provide sufficient information on long-term outcome.[14,15,16,17,18,19] Typically, two to four fractions of 5.5 to 15 Gy each are delivered during one or two insertions and combined with 36 Gy to 50.4 Gy of external beam. Most North American centres use around 18 catheters to deliver a fairly homogenous dose, while many European centres implant fewer catheters (four in Offenbach;[21] eight in Kiel[14]), which results in quite a different dose distribution. Most of the series include intermediate to high-risk patients, with a preponderance of T2 or T3 cancers and intermediate grade (WHO Grade 2, or Gleason 7) histology. The median PSA in most series is a little over 10 ng/ml. The use of adjuvant androgen blockade is variable in the series – 37% in the series from Kiel,[14] and none at all at Royal Oak.[15] With variable length of follow-up, the reported disease-free survival is 80%-

TABLE 1. **Treatment details and patient characteristics in the reported HDR brachytherapy series**

Centre	HDR dose (Gy) fraction	External beam dose (Gy)	N	Median Follow-up (months)	PSA (%)		Stage (%)			Grade (%)		
					<10	>10	T1	T2	T3	1	2	3
Kiel[2]	30/2	40	144	96	41	59	1	67	32	15	49	36
Royal Oak[3]	16.5-23 /3-2	46	207	53	58	42	17	73	10	39	42	19
Seattle[4]	12-16 / 4	50.4	104	46	53	47	30	60	10	79	16	5
Goteborg[5]	20 / 2	50	50	45	60	40	6	68	26	28	60	12
Berlin[6]	18-20 / 2	45-50.4	230	40	Median 12.8		7	35	58	23	60	17
Long Beach[7]	22-26 / 4	39.6-45	200	?	Mean 10		14	65	21	14	75	11
Aachen[8]	18 / 2	36-50.4	45	39	Not stated		9	40	25	9	66	25
Offenbach[9]	20-28 / 4	39.6-45	35	18	28	72	6	75	19	31	52	17
Oakland[10]	24 / 4	36	491	?	Not stated							

TABLE 2. **Disease-free survival and late toxicity rates by HDR brachytherapy series**

Centre	Disease-free survival			Grade 3 late toxicity
	Low risk	Intermediate	High risk	
Kiel[2]	91%	81%	32%-64%	2% urinary 4.1% rectal
Royal Oak[3]	74%			8% urinary 1% rectal
Seattle[4]	89%	84%	46%	8% urinary
Goteborg[5]	84%			4% urinary 2% rectal
Berlin[6]	80% (PSA <10 ng/ml)	59% (PSA > 10 ng/ml)		12.2% urinary
Long Beach[7]	93%			2% urinary 1.5% rectal

93% for patients with low risk cancer (Stage T1 or 2, PSA < 10 ng/ml, Gleason Score 6 or less), 74%-84% for intermediate risk (Gleason 7, or PSA 10%-20%), and 32%-64% for high risk (Stage T3, Gleason 8-10, PSA > 20 ng/ml) Table 2. The reported cause-specific survival rates are 87% to 100%, with local control rates of usually over 90%. For example, the Goteborg series reported biopsy local control in 97% of T1-T2 patients and in 92% of T3.[17] Late urethral stricture is reported in about 8% of men and seems to be technique related. Late rectal or other toxicities are very uncommon. The effect on potency is uncertain.

High dose-rate brachytherapy is a promising method of highly conformal dose escalation in combination with external beam radiotherapy for men with intermediate to high-risk cancers. The limited data on its use comes from single institutions with wide variations in practice. It is currently being evaluated in multi-centre clinical trials both in Canada and by the Radiation Therapy Oncology Group in the United States in men with intermediate risk disease.

Hormone therapy
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In this part of the meeting, emphasis was given to the analysis of results of randomized trials combining hormonal therapy and radiotherapy.

Dr. Padraig Warde gave an updated report on two trials performed by the RTOG and one trial carried out by the EORTC:

RTOG 85-31[23] was a Phase III trial comparing radiotherapy alone versus radiotherapy followed by LHRH analog therapy (goserelin) for life. Eligible patients were those with stage T3 or with pelvic lymph node involvement. Patients who had undergone prostatectomy were eligible if they had a pathological stage T3. A total of 996 patients were randomized with the treatment groups well balanced for prognostic factors. With a median follow-up of 6 years for patients at risk, there is a significant decrease in local failure favoring the combined group (27% versus 37%, $p < 0.0001$). Disease free survival (DFS) with a PSA up to 1.5 ng/ml was also significantly improved in the combined group ($p < 0.0001$). Overall survival at 8-year was not statistically different between arms (49% versus 48%, $p = 0.36$). A subset analysis, however, showed an improved overall survival for centrally reviewed Gleason score 8-10 patients. Overall there was a significant improvement in local failure, freedom from metastasis and biochemical free survival benefiting the combined group. Further follow-up may lead to an improved overall survival as well.

RTOG 92-02[24] compared the use of pelvic radiotherapy preceded by total androgen blockade given for 2 months before radiotherapy and also during radiotherapy versus the same program plus 2 years of adjuvant LHRH analog therapy for patients with locally advanced prostate cancer (T2c – T4) and PSA < 150 ng/ml. More than 1500 patients entered the trial. The median follow-up is about 5 years. Significant improvement was seen in local control, disease free survival and biochemical control for the arm receiving adjuvant therapy. Five-year overall survival was similar between the arms. A subset analysis shows a survival benefit in the adjuvant arm for patients with Gleason score 8-10. Another subset analysis compared RTOG 92-02 results with the results

from the EORTC trial by Bolla et al[25] based on patient selection (see below). Of interest, unlike the Bolla trial there was no overall difference in outcome in this subset of patients (T3-4 or T2 with poorly differentiate tumors – WHO grade 3). Further follow-up is needed for solid conclusions.

EORTC 22863 study[25,26] was a comparison between radiotherapy alone versus radiotherapy plus 3 years of adjuvant LHRH analog therapy. Hormonal therapy started on day 1 of radiotherapy. Eligible patients had locally advanced disease defined as T3 or T4 or T2 with poorly differentiated tumors. At a median follow up time of 66 months, there is an overall survival benefit at 5-year for the group receiving the combined treatment (78% versus 62%, p = 0.0002). Disease free survival was also significantly improved in the radiotherapy + hormonal therapy group.

These three trials show improved disease free survival for patients undergoing combined RT and hormonal therapy in the adjuvant setting. However, only the EORTC study clearly shows an overall survival benefit. It is quite possible that, with further follow-up, both RTOG trials eventually will show improvement in overall survival as well. Of note, only RTOG 92-02 had PSA measurements required prior to enrollment. Radiation doses ranged from 6600 to 7000 cGy.

Dr. Gad Perry presented the preliminary results of a multicentre randomized trial comparing 3 months versus 8 months of neoadjuvant total androgen blockade therapy prior to radiotherapy (6600 cGy) for patients with T1-T3 disease.[27] Median baseline at presentation was 9.7 ng/ml. 50% of the patients had a Gleason score of less than 7. Arms were well balanced. Although the long hormonal arm achieved a lower PSA prior to starting radiotherapy and had more downsizing of the prostate, there was no difference in patterns of failure, including biochemical failure or biopsy results, between the arms. At least in this preliminary analysis, longer use of neoadjuvant hormonal therapy did not alter patterns of failure as compared to a shorter course.

Dr. Himu Lukka reviewed the preliminary results from three randomized trials assessing the role of adjuvant hormonal therapy (Casodex 150 mg daily) in patients with localized disease.[28] Patients with localized or locally advanced disease were randomized to receive Casodex versus placebo in addition to standard of care (radiotherapy, prostatectomy or watchful waiting). More than 8000 patients entered the trial. This preliminary analysis pooled the data from all the three different groups in a single overview. At a median follow-up of about 3 years, the addition of Casodex significantly decreased the objective progression of the disease. Overall survival data was not available. As expected, toxicity was higher in the hormonal arm. Longer follow-up of these patients is needed with reporting of survival endpoints. This large database has the potential to define the potential benefit of adjuvant therapy for patients with low risk and intermediate risk disease.

Hypofractionation

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Dr. Jack Fowler reviewed clinical data, largely derived from the results of external beam radiation and brachytherapy, which lend support to the notion of a low α/β ratio for prostate cancer. These estimates range from 1.2 to 3.1. If the α/β for late responding normal tissues such as rectal mucosa lie above this figure, (and he suggested values of 3-5 Gy) then a therapeutic advantage may be possible from using hypofractionated regimes.

If it is assumed that the prostate α/β is indeed low, it is possible to deduce optimal fractionation schemes that could be taken forward into the clinic for further study.[29,30] Traditional regimes of 35-40 fractions (with fraction sizes of 1.8 Gy – 2 Gy) have disadvantages of inconvenience, but do allow healing of acute reactions to occur during the treatment course. Dr Fowler suggested that a theoretically ideal hypofractionated regime should not be completed in less than approximately 5 weeks, in order to minimize the risk of consequential late reactions. Such regimes should additionally employ at least five fractions. It was noted that UK series had previously employed 3600 cGy in six weekly fractions, with apparent good results. Modeling results from published clinical series, Dr Fowler suggested that an ideal regime might use 4700 cGy in 10 fractions (over 5 weeks), which he predicted might be biologically equivalent to 8400 cGy in 42 fractions.

Dr. Patrick Kupelian presented a large series from the Cleveland Clinic, Ohio. Over 700 men have been treated with an IMRT-based hypofractionated schedule of 7000 cGy in 2.5 Gy fractions, which he estimated is equivalent to 8300 cGy at 1.8 Gy fractions.[31] The radiation delivery technique described in this study has small margins of 4 mm posteriorly, 5 mm anteriorly and 8 mm in other directions, with daily correction of prostate positioning by means of a trans-abdominal ultrasound localization device. He

reviewed results of 321 men treated with this technique, in comparison with 287 men treated with conventional fractionation at the same institution (7800 cGy in 34 fractions). In both groups short-term androgen deprivation was used in about 60% of cases. It was noted that planning target volumes were somewhat smaller in the hypofractionation group, where median follow-up was 21 months.

Acute toxicity was comparable to standard fractionation (grade 2+ rectal toxicity 12% v. 18%; grade 2+ urinary toxicity 20% v. 19% for hypofractionated versus conventional respectively). The actuarial late rectal grade 3 toxicity observed at 36 months was 2% after hypofractionation versus 4% after conventional fractionation, (p=0.36). Rectal dose/volume histogram constraints are enforced in the derivation of the IMRT plan. A quality of life study[32] also presented by Dr Kupelian showed decreased bowel bother for those treated with hypofractionation compared with standard fractionation (p=0.041). Although he cautioned that estimates of biochemical control are to be interpreted with care due to short follow-up, early (3-year projected) rates showed results at least as good as

TABLE 3. Ongoing clinical trials

Principal investigator/ Study location	**Research objective**	**Study design**	**Comment**
Dr. Gerard Morton, Toronto-Sunnybrook Regional Cancer Centre	To evaluate use of high dose rate brachytherapy boost (1000 cGy x 2) in combination with external radiotherapy (4500 cGy) in intermediate risk patients	Phase II	Study will capitalize on the use of brachytherapy to deliver high dose radiation to the prostate
Dr. Charles Catton, Princess Margaret Hospital	To evaluate hypofractionated IMRT (6000 cGy/20 fractions) in intermediate risk patients	Phase II	Results will form the basis for a future phase III trial
Dr. Michael McKenzie co-PI, British Columbia Cancer Agency	To evaluate combination chemotherapy (taxotere), hormone therapy and radiotherapy in extreme risk patients with localized disease	Phase II	Results will form the basis for a future phase III trial
Dr. Jim Morris, British Columbia Cancer Agency	To evaluate androgen suppression and elective nodal radiation followed by high dose conformal boost or 125I brachytherapy boost in intermediate or high risk patients	Phase II/III sequential trial	Phase II trial accrual is complete
Dr. Abdenour Nabid, Sherbrooke, Quebec	To evaluate total androgen blockade (goserelin + bicalutamide) plus radiation (2 arms) vs. radiation alone in intermediate risk patients	Phase III	Three arm trial with the additional arm evaluating lower dose radiation + androgen blockage
Dr. Abdenour Nabid, Sherbrooke, Quebec	To evaluate length of total androgen blockade prior to combined nodal and prostate radiation in high risk patients	Phase III	Two arm trial comparing 36 months versus 18 months of hormone treatment

TABLE 4. Proposed clinical trials. These trials were discussed as possible future trial opportunities in radiation oncology for prostate cancer

Proposal	Study Design	Comment
A study evaluating salvage, low dose rate brachytherapy in patients with local recurrence following radiotherapy	Phase II	Study would provide valuable information on salvage brachytherapy and toxicity
A study evaluating the optimal length of neoadjuvant hormone therapy in high risk patients	Phase III	Await results from RTOG 99-10 prior to design
A study evaluating hypofractionated IMRT vs. standard conformal radiotherapy in intermediate risk patients	Phase III	Proposed by Dr. Charles Catton
A study evaluating high dose radiotherapy (8000 cGy) vs. pelvic radiotherapy and high dose rate boost in intermediate risk patients	Phase III	Further discussion would be required

conventionally fractionated patients.

Dr. Charles Catton described the ongoing Canadian experience at the Princess Margaret Hospital. Intermediate risk prostate cancer patients are being treated with IMRT in an expanded phase 2 trial to a dose of 6000 cGy in 20 fraction over 4 weeks. Daily image matching on implanted fiducial markers is performed to minimize errors from set-up and target organ motion. He presented early data from 25 patients so treated. Acute grade 2+ toxicity was 25% (GU) and 8% (GI), and grade 3+ toxicity was 0% (GU) and 4% (GI). For the 15 patients with at least 3 months follow-up, no serious late toxicity had been observed. The trial is ongoing with a planned accrual of 200 men, before consideration of further dose escalation within a 20 fraction regime.

Dr. Himu Lukka described the completed PR 5 study on behalf of the investigators.[33] This is the only randomized trial of conventional (6600 cGy/33 fractions) versus hypofractionated (5250 cGy/20 fractions) external radiation to date. The study was completed in December 1998, after 936 patients had been randomized. Minimum follow-up was 4 years. Prior to analysis of the trial, the study committee had determined that the primary end point of the trial should be PSA relapse, rather than 2-year biopsy positivity rates, as had been the initial intent. This decision had been based on modest concordance between reviewing pathologists, and a general appreciation within the genitourinary community that the prognostic value of apparently positive biopsies at this time-frame post-radiation could be unreliable. New information regarding alternative PSA-relapse definitions was also forthcoming. Although these would be unlikely to affect any differences in outcome between the two arms of a randomized trial not employing androgen ablation, it had been decided that the Houston[34] (nadir plus 2ng/ml) and Vancouver[35] criteria would be analyzed in addition to the ASTRO definition,[36] which would become the new primary trial endpoint. Dr. Lukka expressed hope that the trial results (whether or not they show an advantage to one or other arm) will add new data points to allow α/β calculations, and be a springboard for future Canadian trials.

Clinical trials
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Opportunities for clinical trials were discussed throughout the meeting. Key clinical trials that were in progress or proposed as ideas for future investigations are highlighted in Table 3 and Table 4. These trials were not supported by the conference but were discussed in effort to improve the management of prostate cancer.

Conclusion

The participants expressed strong support for evaluating a hypofractionated radiation regimen using IMRT in a national randomized trial. Enthusiasm for further research involving HDR brachytherapy in intermediate and high-risk patients was also shown. Although hormone therapy continues to play an important role in the treatment of prostate cancer, clarification of optimal timing, duration and appropriate patient population is necessary and will be forthcoming in future clinical trials. □

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