Prostate cancer: risk categories and role of hormones and radiotherapy

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The Genito-Urinary Radiation Oncologists of Canada (GUROC) have produced a consensus statement on radiotherapy in prostate cancer. This paper summarizes the consensus statement with regard to risk grouping and the role of hormones and radiotherapy. Survival is the most important outcome in the assessment of patients treated with radiotherapy. Other outcomes of interest include disease-free survival, metastatic-free survival, local control, biochemical measures, toxicity, efficacy, and quality of life. Risk groupings based on prognostic data are increasingly used in the management of prostate cancer. These groupings have been correlated to prognosis in several studies, and are helpful in identifying optimum treatments, and as a research tool to evaluate new treatments and modalities. Adjuvant hormone treatment with radiotherapy has been demonstrated in two studies (Bolla and RTOG 85-31) to be beneficial in patients with locally advanced prostate cancer. Neoadjuvant hormone treatment in patients with low- and intermediate-risk disease is being evaluated in a RTOG study and its utility in these patients will be clarified when the study results are available. The GUROC consensus statement recommends that patients with high-risk non-metastatic prostate cancer be treated with adjuvant hormone therapy for 2–3 years. Part of this hormone treatment may be administered in a neoadjuvant fashion. Adjuvant hormone treatment should not be routinely used in low- and intermediate-risk prostate cancer. Neoadjuvant hormone treatment is recommended prior to radiotherapy in patients with bulky tumors. The results of ongoing research will further clarify the use of hormone treatment with radiotherapy.

Key Words: hormone therapy, radiotherapy, prostate cancer, risk categories

Introduction

The Genito-Urinary Radiation Oncologists of Canada (GUROC) held a consensus meeting in November 2000 where they reached consensus on four key controversial prostate cancer radiotherapy topics. These topics included:

a) Risk groupings
b) Brachytherapy
c) Conformal Radiotherapy
d) Role of Hormones and Radiotherapy

The full consensus statement has been published in The Canadian Journal of Urology Volume 8(4); August 2001.

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The presentation at the 2002 Uro Oncology Congress summarized the consensus statement on two of these areas of controversy – risk grouping and role of hormones and radiotherapy.

Outcomes

The most important outcome in the assessment of patients receiving radiotherapy for prostate cancer is survival. Other outcomes of interest are summarized in Table 1. Given the long natural history of prostate cancer surrogate outcomes such as PSA failure have been used to evaluate efficacy.

Risk grouping

Risk groupings using a combination of factors/criteria are being increasingly used in management of prostate cancer. These risk groupings have been developed based on prognostic data. These groupings are helpful in identifying optimum treatment modality or modalities. It may also help identify patients suitable for more intensive treatment while in other patients treatment may be minimized. Risk grouping is also useful as a research tool to evaluate new treatments or modalities.

Until recently prostate cancer has been classified into localized and locally advanced prostate cancer using traditional TNM criteria only Table 2. More recently physicians have incorporated other prognostic factors (PSA and Gleason Score) to T-staging and developed risk groupings – low, intermediate and high risk. The risk groupings and criteria used are shown in Table 2.

Table 3 summarizes the specifics of the three risk grouping factors adopted by GUROC. Several studies have correlated these risk groupings to prognosis. The risk grouping agreed to by GUROC included:

TABLE 1. **Prostate cancer treatment**

Outcomes
- Toxicity
- Efficacy
  - Survival
  - Disease free survival
  - Metastatic free survival
  - Local control
  - Biochemical (bNED)
- QOL

TABLE 2. **Prostate cancer risk groupings**

Traditional
- Extent of disease
- Localized
- Locally advanced

Criteria
- TNM staging

Emerging risk groupings
- Low risk
- Intermediate risk
- High risk

Criteria
- T staging
- PSA
- Gleason score

TABLE 3. **Risk grouping: consensus**

	T_{1-2}			T_3	Key
	PSA ≤10	**PSA 10.1-20**	**PSA >20**		
Gl Score ≤ 6	($T2_a$)				Low Risk
Gl Score 7					Inter. Risk
Gl Score ≥8					High Risk

1. Low-risk; must have *all* of the following:
   - PSA ≤ 10 ng/mL
   - Gleason ≤ 6
   - Stage T2a or less

2. Intermediate-risk; must have *all* of the following if *not* low-risk:
   - PSA ≤ 20 ng/mL
   - Gleason < 8
   - Stage T1/T2

3. High-risk; must have *any* of the following:
   - PSA > 20 ng/mL
   - Gleason ≥ 8
   - Stage ≥ T3a

Role of hormones and radiotherapy

Two adjuvant hormone studies with radiotherapy (Bolla and RTOG 85-31) have demonstrated a benefit with the use of hormones in patients with locally advanced prostate cancer. The Bolla study, (EORTC 22863) Table 4 and 5 demonstrated a survival advantage with the use of adjuvant hormones. The RTOG study 85-31, Table 6 and 7 did not demonstrate a survival advantage but demonstrated a statistically significant reduction in distant metastases and an improvement in bNED rates with the use of adjuvant hormones. It is difficult to be sure if the differences in survival results between these two studies were due to differences in the two studies or due in part to the differences in prostate cancer presentation between Europe and North America.

The role of neoadjuvant hormones with radiotherapy in patients with bulky T2-4 tumor has been evaluated in a randomized study (RTOG 86-10). The hormones in

TABLE 4. **EORTC 22863: Study design**

Hormone therapy adjuvant to radiotherapy: EORTC 22863: Study design

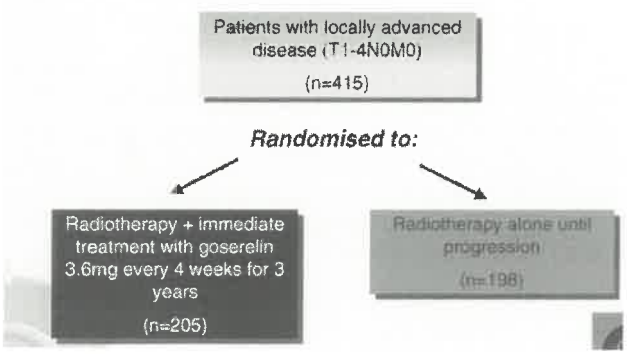
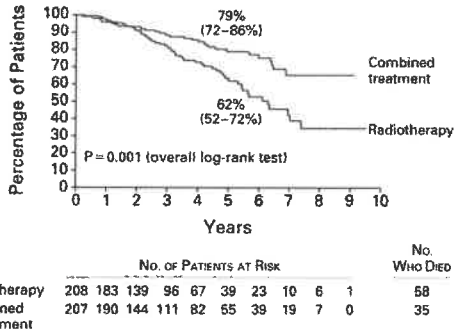


TABLE 5. **EORTC 22863** (Reprinted with permission)



No. of Patients at Risk											No. Who Died
Radiotherapy	208	183	139	96	67	39	23	10	6	1	58
Combined treatment	207	190	144	111	82	55	39	19	7	0	35

Kaplan–Meier Estimate of Overall Survival.
The overall survival rate at five years was 79 percent (95 percent confidence interval, 72 to 86 percent) for the combined-treatment group and 62 percent (95 percent confidence interval, 52 to 72 percent) for the group treated only with radiotherapy.

Bolla M et al. Improved Survival in Patients with Locally Advanced Prostate Cancer Treated with Radiotheapy and Goserelin. N Engl J Med 1997;337:295-300.

TABLE 6. **RTOG 85-31: Study design**

RTOG 85-31: Study design

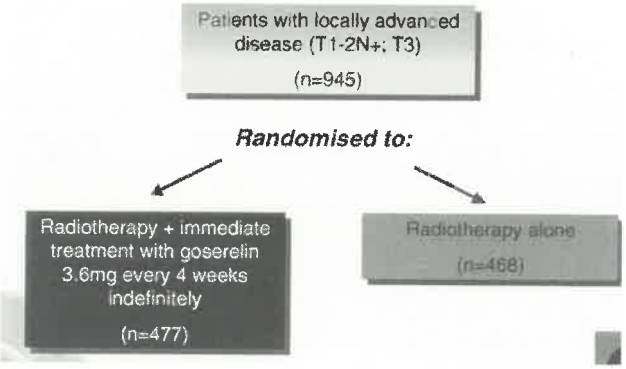


TABLE 7. **RTOG 85-31**

	RT	RT + Hormones
Local failure	37%	23% p<0.0001
Distant metasteses	37%	27% p<0.0001
bNED	8%	32% p<0.0001
Overall survival	no difference	except in Gleason 8-10

Pilepich et al ASTRO 2000

this case were given for two months before and two months during the radiotherapy, Table 8 and 9. There was no survival advantage demonstrated though a statistically significant difference in distant metastases was noted. The role of neoadjuvant hormone treatment in patients with low and intermediate risk patients will be clarified when the results of RTOG 94-08 are available.

TABLE 8. **Neoadjuvant hormones. RTOG 86-10**

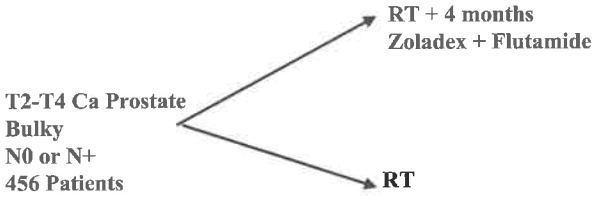


TABLE 9. **Hormonal therapy, neoadjuvant to radiotherapy. RTOG 86-10**

Local failure	37% vs 48%	p=0.002
Distant metastases	34% vs 48%	p=0.03
NED	35% vs 23%	p=0.0018
NED biochemical	23% vs 8%	p=<0.0001
Survival	51% vs 43%	NS

RTOG 9202 has recently been published. The design of the study is shown in Table 10. Patients with locally advanced prostate cancer were randomized after neoadjuvant hormones and radiotherapy to adjuvant hormones or no further therapy. This study also did not demonstrate a survival advantage except for a sub-group of patients with Gleason score 8-10. A small difference in distant metastatic rate was noted but of uncertain statistical significance. Details of the published results are shown in Table 11.

TABLE 10. **RTOG 92-02: Study design**

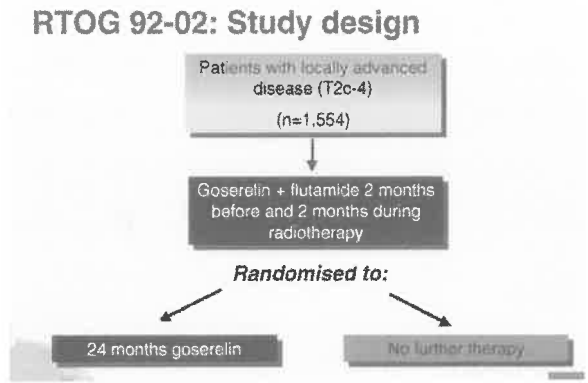


TABLE 11. **RTOG 92-02**

	RT + 4 months hormones	RT = 24 months hormones
Local failure	11.8%	5.6%
Distant metastases	16%	10%
bNED	22%	49%
Overall survival	No difference	Gleason 8-10 80% vs. 69% p=0.02

Hanks et al ASTRO 2000

TABLE 12. **Concensus statement**

	Neoadjuvant hormones	Adjuvant hormones
Low risk	not routinely	not routinely
Intermediate risk		
bulky	yes	not routinely
non bulky	not routinely	not routinely
High risk	reasonable	yes

TABLE 13. **Highlights of areas of current research**

Role of neoadjuvant hormones in low/intermediate risk patients
Length of neoadjuvant hormones
Length of adjuvant hormones
Role of adjuvant hormones in intermediate risk patients
Role of hormones with high doses of RT

The consensus statement from GUROC is shown in Table 12. It was recommended that patients with high-risk non-metastatic prostate cancer be treated with prolonged (up to 2-3 years) adjuvant hormonal therapy. Part of this hormonal treatment may be given in a neoadjuvant fashion. Adjuvant hormonal treatment should not be routinely used in low and intermediate risk prostate cancer. Neoadjuvant hormonal treatment would be recommended prior to radiotherapy in patients with bulky tumors. The role of neoadjuvant hormones in other patients with intermediate and low risk prostate cancer is unclear.

The current advances in management of prostate cancer have occurred through research and clinical trials. Table 13 highlights some of the areas of current research. The results of these studies will help further advance the management of prostate cancer. □