Radiotherapy: Clinical question 2

A systematic review was undertaken to address the clinical question:

What is the evidence for the effect of radiotherapy in palliation of soft tissue disease of EBRT:

(a) to the prostate for symptom treatment in locally advanced disease?
(b) to local metastases such as the lymph nodes for symptom treatment such as lymphoedema and painful lymph nodes?

Methods

Initial Literature Search

Medline (1966 – October 2006), EMBASE (1988 – October 2006) and CINAHL (1982 – October 2006) databases were searched. The search contained keywords and subject headings, such as “radiation.mp.” and “exp radiotherapy/” respectively. This search was coupled with keywords and subheadings aimed at identifying prostate cancer-based research, such as “exp prostatic neoplasms/”. The Cochrane Collaboration randomised controlled trial search filter was then applied. All citations from this search were reviewed for relevant articles. A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all articles obtained were reviewed and clinical trial registers (http://www.who.int/ictrp/en/ and http://www.cancer.gov/) searched for additional relevant clinical trials.

Inclusion Criteria

Included studies:

- Examined external beam radiotherapy including three dimensional conformal radiotherapy (3D CRT) and hemibody radiotherapy but not particle beam radiotherapy, brachytherapy or radioisotopes;
- Employed a relevant control group (e.g., different radiation doses or dose schedules, other treatments such as hormone therapy or watchful waiting);
- Included patients who had clinical stage T3 prostate cancer and beyond;
- Published in English;
- Published prior to April 1 2006.
Additional Clinical Question Specific Search

The randomised controlled trial filter was removed and the resulting search was coupled with a search aimed at identifying palliative treatment with keywords and sub-headings aimed at identifying palliation such as “palliati$.mp.” A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all articles obtained were reviewed for other relevant articles.

Revised inclusion criteria

Included studies:

- Examined external beam radiotherapy but not adjuvant hyperthermia, brachytherapy or radioisotopes;
- Were case series or higher evidence;
- Included prostate cancer patients treated with palliative intent for loco-regional symptoms (pain, urinary obstruction, edema, haematuria) or local progression;
- Published in English;
- Published prior to April 1 2006 or in the case of systematic reviews, reviewed only papers published prior to April 2006.

Results

Results of Literature Search

The initial combined Medline, EMBASE and CINAHL database search identified 3306 citations. Titles and abstracts were examined, and 148 articles were retrieved for a more detailed evaluation. No prostate cancer specific randomised controlled trials were identified for clinical question 2. Thus an additional clinical question specific search was undertaken with revised inclusion criteria as determined by the Radiation Oncology Working Party subgroup (see above).

Figure 1 outlines the process of identifying relevant articles for question 2.

The clinical question 2 specific database search identified 167 citations. Titles and abstracts were examined, and 25 articles were retrieved for a more detailed evaluation. Examination of the reference lists of these articles identified another eight articles for retrieval. Ten case series were included in the systematic review.

The reference and characteristics of the excluded articles are included in Appendix B. In summary, most articles were excluded because they were not systematic reviews or did not examine radiotherapy as a treatment for the symptoms of loco-regional progression.

A relevant case series published after 1st April 2006 was found by hand searching of relevant journal titles and is described in Appendix C.
Figure 1. Process of inclusion and exclusion of studies for this systematic review

Study characteristics
Characteristics of included studies are described in table 1
**Table 1. Case series studies examining EBRT for loco-regional symptom palliation: study characteristics and results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Reason for Radiotherapy</th>
<th>Radiotherapy</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carlton 1972</strong></td>
<td>Prostate cancer with large extracapsular lesions or metastatic disease Hormone naïve and hormone refractory</td>
<td>Palliation of local symptoms Haemorrhage n = 7 Bladder neck obstruction n = 40 Ureteral obstruction resulting in hydronephrosis n = 11</td>
<td>4,000 – 4,500 rads</td>
<td>Palliation</td>
<td>7/7 Haemorrhage ceased 20/40 Bladder neck obstruction relieved 8/11 alleviation of ureteral obstruction 16% mild proctitis 2 % severe proctitis 18% mild cystitis 2 % severe cystitis</td>
</tr>
<tr>
<td><strong>Kraus 1972</strong></td>
<td>Prostate cancer extracapsular and more advanced (stage C and D) Hormone refractory minimum n = 22</td>
<td>Palliation of local symptoms Haematuria n = 11 Rectal symptoms n = 6 Ureteral obstruction n = 5</td>
<td>2,250 – 6,600 rads (200 – 250 rad fractions) Field encompassed gross tumour</td>
<td>Palliation</td>
<td>Mean follow-up = 11 months 11/11 alleviation of haematuria 6/6 marked alleviation of rectal symptoms 4/5 Alleviation of ureteral obstruction 18/33 minor complications (dermatitis, proctitis and dysuria) 1/33 rectourethral fistula</td>
</tr>
<tr>
<td><strong>Green 1974</strong></td>
<td>Prostate tumour encroaching on rectal or sigmoidal wall Prior prostatectomy n = 4 Hormone (oestrogen) resistant n = 8 Starting oestrogen therapy n = 1</td>
<td>Palliation of rectal and sigmoid disorders caused by prostate cancer Rectal symptoms n = 11</td>
<td>1,600 – 7,600 R (800 R per week) Minimum field size = 15 x 15cm designed to encompass pelvic tumour</td>
<td>Palliation</td>
<td>10/11 alleviated rectal symptoms 0/2 ureteral obstruction alleviated 3/3 alleviated of slow stream 0/1 alleviated of dysuria 2/3 alleviated of haematuria 1/1 improved bladder capacity 1/1 severe long term cystitis (7,200 R dose) 1/11 rectal damage requiring colostomy (7,600R dose)</td>
</tr>
<tr>
<td><strong>Megalli 1974</strong></td>
<td>Prostate cancer with ureteral obstruction Hormone refractory n = 8 Hormone naïve ? n = 2</td>
<td>Ureteral obstruction</td>
<td>5,000 – 6,000 rads (200 rad fractions) 15 x 15 cm fields</td>
<td>Response (Improvement in pyelogram, BUN and serum creatinine)</td>
<td>10/10 responded 6/10 complete response Maximum effect 2-6 months after completing radiotherapy</td>
</tr>
<tr>
<td><strong>Michigan 1977</strong></td>
<td>Prostate cancer with hormone (orchiectomy or oestrogen) refractory upper urinary tract obstruction</td>
<td>Upper urinary tract obstruction</td>
<td>4,000 – 5,500 rads over 4 – 5.5 weeks</td>
<td>Radiographic evidence of a response</td>
<td>2/8 improved 2/8 radiotherapy terminated as obstruction worsened</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Symptom Palliation</td>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fossa 1987</td>
<td>Hormone (orchiectomy and/or oestrogens) refractory prostate cancer with pelvic pain and/or micturition problems</td>
<td>Median = 50 Gy (36-52 Gy) (2 Gy fractions) Field included the prostatic tumour and the pelvic lymph nodes</td>
<td>Symptom palliation 5/6 improvement in pelvic pain 3/5 improvement with micturition 1/2 improvement in pelvic pain + micturition 2/3 improvement in ureteric stenosis 1/2 improvement in rectal stenosis 0/1 improvement in rectal + ureteric stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 8 (Norway)</td>
<td>11/19 distant metastases</td>
<td></td>
<td>Median survival 12 months with distant metastases 24 months no distant metastases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Symptom Palliation</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynaston 1990</td>
<td>Hormone refractory prostate cancer with urinary symptoms</td>
<td>3500 cGy (usually 15 x 233 cGy fractions) Or 2400 cGy (weekly 800 cGy fraction)</td>
<td>Symptom palliation 15/17 improvement in micturition problems (5/17 asymptomatic) 13/13 improvement in haematuria (11/13 asymptomatic)</td>
</tr>
<tr>
<td>(UK)</td>
<td>TURP n = 17</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Symptom Palliation</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez 1993</td>
<td>Prostate cancer with local symptoms - Most hormone refractory</td>
<td>Field size 12 x 12 - 15 cm</td>
<td></td>
</tr>
<tr>
<td>(USA)</td>
<td>N = 26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Symptom Palliation</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furuya 1999</td>
<td>A sub group of patients with hormone refractory prostate cancer with local progression but no evidence of distant progression Prior to hormone therapy T3-4 or N+ n = 3 or M+ n = 8 No prostatectomy or previous radiotherapy</td>
<td>Local progression ( &gt; 25% increase in prostate size) 7/11 no symptoms 1/11 rectal discomfort 3/11 dysuria and/or bleeding 50 – 66.6 Gy to primary lesion 4-field box technique</td>
<td>Symptom palliation 1/1 rectal discomfort alleviated 3/3 dysuria and/or bleeding alleviated Symptom progression 11/11 no local symptoms after radiotherapy (7 - 64 month survival) Toxicity Complications 2/11 pollakisuria 3/11 diarrhoea May be bias is selection of patients for radiotherapy</td>
</tr>
<tr>
<td>(Japan)</td>
<td>N = 11 Hormone therapy continued</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Hernes 2003 (Norway) | Hormone refractory prostate cancer with symptomatic pelvic tumours | Palliation of symptomatic pelvic tumour  
No distant metastases  
Micturition problems n = 12  
Haematuria n = 4  
Rectal stenosis n = 4  
Lymphoedema n = 2  
Pelvic soft tissue pain n = 13 | 50-60 Gy (2 Gy fractions)  
(n = 110) or  
30 Gy (3 Gy fractions)  
Regime mostly based on radiotherapy resources and patient's general condition  
Target = pelvic tumour manifestation based on CT scans + 2 cm safety margin | Survival  
Median overall survival:  
No distant metastases  
19 months (95% CI, 7-30)  
With distant metastases  
9 months (95% CI, 7-11) | Palliation  
Palliation efficacy evaluation not possible in most cases as follow-up information missing.  
Authors note “efficacy of palliative pelvic RT should be explored in prospective clinical trials” |
|---|---|---|---|---|
| No distant metastases n = 35  
With distant metastases n = 97 | Previous TURP n = 80 |  |  |  |

PAP = prostatic acid phosphatase; BUN = Blood urea nitrogen

Due to an absence of follow-up information in Hernes et al., 2003 we were unable to extract the results for local palliative radiotherapy.
Table 2: Summary of results from case series for palliative loco-regional EBRT symptom responses and toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Haematuria response</th>
<th>Urethral /bladder neck obstruction /micturition problems response</th>
<th>Ureteral obstruction/hydronephrosis /uretic stenosis response</th>
<th>Rectal symptoms/stenosis response</th>
<th>Pelvic or perineal pain response</th>
<th>Toxicity (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlton 1972</td>
<td>7/7 (complete)</td>
<td>20/40</td>
<td>8/11</td>
<td></td>
<td></td>
<td>2% severe cystitis 2% severe proctitis</td>
</tr>
<tr>
<td>Kraus 1972</td>
<td>11/11</td>
<td>4/5</td>
<td>6/6</td>
<td></td>
<td></td>
<td>1/33 rectourethral fistula</td>
</tr>
<tr>
<td>Green 1974</td>
<td>2/3</td>
<td>4/5</td>
<td>0/2</td>
<td>10/11</td>
<td></td>
<td>1/11 severe cystitis 1/11 rectal damage</td>
</tr>
<tr>
<td>Megalli 1974</td>
<td></td>
<td>10/10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michigan 1977</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2/8 obstruction worsened</td>
</tr>
<tr>
<td>Fossa 1987</td>
<td></td>
<td>3/5</td>
<td>2/3</td>
<td>1/2</td>
<td>5/6</td>
<td></td>
</tr>
<tr>
<td>Kynaston 1990</td>
<td>13/13</td>
<td>15/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perez 1993</td>
<td>5/5</td>
<td>6/8</td>
<td>2/4</td>
<td></td>
<td>5/5</td>
<td></td>
</tr>
<tr>
<td>Furuya 1999</td>
<td>3/3</td>
<td></td>
<td></td>
<td></td>
<td>3/5 (complete)</td>
<td></td>
</tr>
</tbody>
</table>
References for Question 2


Appendix A: Search Strategy
Radiotherapy – Initial Search


Search History (results)
1 exp prostatic neoplasms/ (104559)
2 (prostat$ adj3 (cancer$ or carcinoma$ or malig$ or tumo?r$ or neolpa$ or metastast$ or adeno$)).mp. (118827)
3 1 or 2 (118827)
4 exp radiotherapy, high energy/ (15030)
5 exp radiotherapy/ (202843)
6 exp radiotherapy dosage/ (69402)
7 exp hemibody irradiation/ (105828)
8 exp lymphatic irradiation/ (105890)
9 exp radiotherapy, adjuvant/ (34570)
10 exp radiotherapy, intensity modulated/ (192)
11 exp whole body irradiation/ (13002)
12 exp dose fractionation/ (7778)
13 exp radiotherapy, computer assisted/ (9916)
14 exp radiotherapy, intraoperative/ (16)
15 radiotherapy.mp. (205572)
16 irradiation.mp. (175718)
17 radiation.mp. (422803)
18 or/4-17 (639868)
19 randomized controlled trial.pt. (239241)
20 controlled clinical trial.pt. (77271)
21 randomized controlled trials/ (190228)
22 double blind method/ (149363)
23 random allocation/ (80126)
24 single blind method/ (16988)
25 or/19-24 (581668)
26 animals/ not (animals/ and humans/) (3130740)
27 25 not 26 (558382)
28 clinical trial.pt. (482609)
29 exp clinical trial/ (961938)
30 (clinic$ adj25 trial$).tw. (248232)
31 cross-over studies/ (37372)
32 (crossover or cross over or cross-over).tw. (68839)
33 ((singl$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).tw. (165202)
34 placebos/ (95398)
35 placebo$.tw. (190878)
36 random$.tw. (701981)
37 research design/ (234669)
38 or/28-37 (1748382)
39 38 not 26 (1684039)
40 27 or 39 (1715931)
41 3 and 18 and 40 (4752)
42 remove duplicates from 41 (3635)
43 limit 42 to english (3306)
Radiotherapy – Question 2 Specific Search


Search History (results)

1  exp prostatic neoplasms/ (116701)
2  (prostat$ adj3 (cancer$ or carcinoma$ or malig$ or tumo?r$ or neopla$ or metastas$ or adeno$)).mp. (132902)
3  1 or 2 (132902)
4  exp radiotherapy/ (235304)
5  exp lymphatic irradiation/ (135578)
6  radiotherapy.mp. (232382)
7  irradiation.mp. (198506)
8  radiation.mp. (485318)
9  or/4-8 (712682)
10  palliative$.mp. (83413)
11  (symptom$ adj3 control).mp. (10899)
12  exp palliation/ (20460)
13  10 or 11 or 12 (92716)
14  3 and 9 and 13 (1156)
15  benign prostatic hyperplasia.mp. (12743)
16  (local progression or inguinal or pelvic or urinary or ureter$ or urethra$ or perineal).mp. (637109)
17  (urinary obstruction or bleeding or h?ematuria or edema or rectal).mp. (479971)
18  (urinary obstruction or bleeding or hematuria or haematuria or edema or rectal).mp. (505809)
19  16 or 18 (1100236)
20  rectal toxicity.mp. (235)
21  (radiotherapy adj4 toxicity).mp. (1142)
22  20 or 21 (1356)
23  19 not 22 (1099773)
24  14 not 15 (1149)
25  24 and 23 (297)
26  remove duplicates from 25 (224)
27  limit 26 to english language (173)
28  limit 27 to yr="1902 - 2006" (167)
Appendix B: Excluded Studies

Radiotherapy – Question 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aass 1994</td>
<td>Review article</td>
</tr>
<tr>
<td>Ampil 1989</td>
<td>4/6 prostate cancer patients started concurrent hormone therapy</td>
</tr>
<tr>
<td>Bailey 2002</td>
<td>Radiotherapy not described and unclear as to which if any patients received radiotherapy</td>
</tr>
<tr>
<td>Barrass 2005</td>
<td>Review article</td>
</tr>
<tr>
<td>Clarke 2003</td>
<td>Review article</td>
</tr>
<tr>
<td>Clarke 2006</td>
<td>Review article</td>
</tr>
<tr>
<td>Esper 1997</td>
<td>Review article</td>
</tr>
<tr>
<td>Fournier 1996</td>
<td>Review article</td>
</tr>
<tr>
<td>Gibbons 1979</td>
<td>Does not document effect on symptoms</td>
</tr>
<tr>
<td>Hernes 2000</td>
<td>Does not examine the effects of radiotherapy</td>
</tr>
<tr>
<td>James 2006</td>
<td>Review article</td>
</tr>
<tr>
<td>Jenkins 1996</td>
<td>No prostate cancer patients</td>
</tr>
<tr>
<td>Kalapurakal 2003</td>
<td>Examined effects of radiotherapy combined with hyperthermic therapy</td>
</tr>
<tr>
<td>Kawakami 1993</td>
<td>Japanese language publication</td>
</tr>
<tr>
<td>Konski 2005</td>
<td>Review article</td>
</tr>
<tr>
<td>Korb 2000</td>
<td>Review article</td>
</tr>
<tr>
<td>Lankford 1995</td>
<td>Does not document effect on existing symptoms</td>
</tr>
<tr>
<td>Ok 2005</td>
<td>Review article</td>
</tr>
<tr>
<td>Sanguineti 2004</td>
<td>Patients mostly asymptomatic; Does not document effect on symptoms</td>
</tr>
<tr>
<td>Smith 1999</td>
<td>Review article</td>
</tr>
<tr>
<td>Sogani 1987</td>
<td>Review article</td>
</tr>
<tr>
<td>Spanos 1989</td>
<td>Includes various primaries: Results not stratified by cancer type.</td>
</tr>
<tr>
<td>Swanson</td>
<td>Review</td>
</tr>
</tbody>
</table>
References for excluded studies


Jenkins CN, McVor J (1996) Survival after embolization of the internal iliac arteries in ten patients with severe haematuria due to recurrent pelvic carcinoma.[see comment]. Clinical Radiology 51: 865-868


Korb L (2000) Radiotherapy for the palliation of prostate cancer. [Review] [31 refs]. Seminars in Surgical Oncology 18: 75-79


Appendix C: Relevant post 2006 publications

Table 1. Case series examining EBRT for loco-regional symptom palliation: study characteristics and results

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Reason for Radiotherapy</th>
<th>Radiotherapy</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hindson 2007</td>
<td>51% M1</td>
<td>Hormone resistant prostate cancer with prostate and/or pelvic symptoms</td>
<td>Palliation of local symptoms n = 18</td>
<td>30-70Gy Median = 60 Gy 2-3Gy fractions</td>
<td>Palliation Survival Toxicity Mean follow-up = 5.2 months</td>
</tr>
<tr>
<td>(Australia)</td>
<td></td>
<td>12 patients had undergone TURP in previous 6 months but despite this had worsening symptoms</td>
<td>Bladder outlet obstruction</td>
<td>4/5 Haematuria ceased or stable 18/30 (60%) Bladder outlet obstruction symptoms improved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haematuria n = 5 Bladder outlet obstruction + haematuria n = 3 Bladder outlet obstruction + pelvic pain n = 2 Bladder and rectal outlet obstruction n = 5 Bladder and rectal outlet obstruction + pelvic pain n = 2</td>
<td>18/30 (partial)</td>
<td>In those patients who also had bladder outlet obstruction symptoms it is unclear as to how haematuria, pelvic pain and rectal obstruction symptoms responded</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Summary of case series results for palliative loco-regional EBRT symptom responses and toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Haematuria response</th>
<th>Bladder outlet obstruction response</th>
<th>Rectal symptoms/stenosis response</th>
<th>Pelvic or perineal pain response</th>
<th>Toxicity (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hindson 2007</td>
<td>3/5 (complete)</td>
<td>18/30 (partial)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not reported

References – Relevant post April 2006 studies