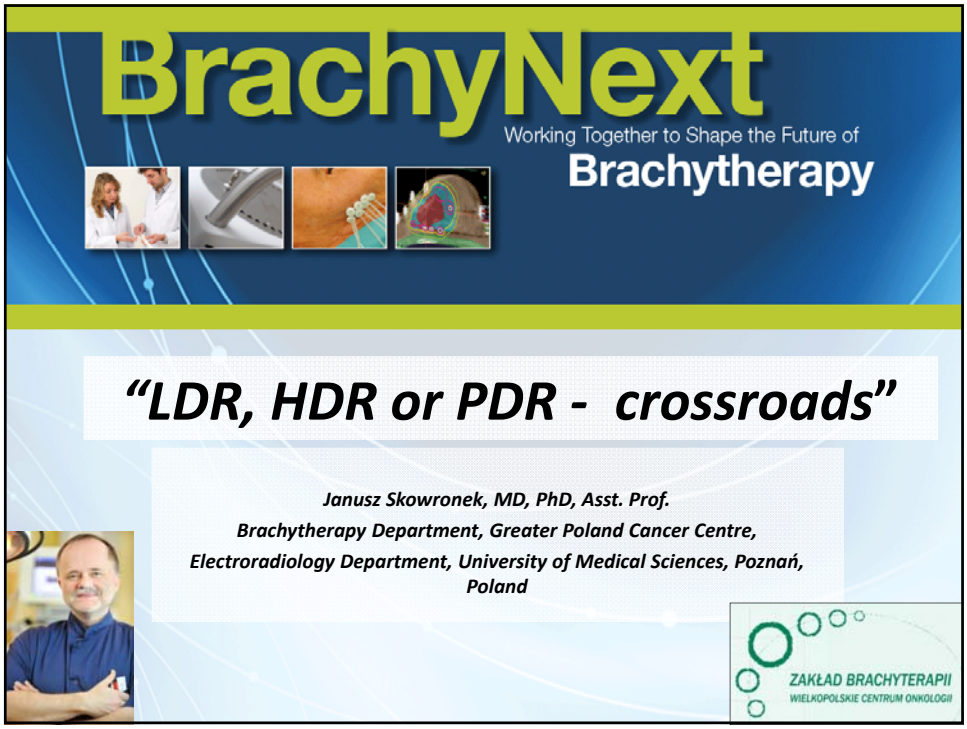


"LDR, HDR or PDR - crossroads"

Janusz Skowronek, MD, PhD, Asst. Prof.
Brachytherapy Department, Greater Poland Cancer Centre,
Electroradiology Department, University of Medical Sciences, Poznań, Poland

ZAKŁAD BRACHYTERAPII
WIELKOPOLSKIE CENTRUM ONKOLOGII

Brachytherapy of prostate cancer

Greater Poland Cancer Centre, Poznań (2006 - 2014):

- **HDR brachytherapy – 2398 applications**
- **Permanent implants (since 2008) – 83 patients**
  (*no reimbursement*)

Permanent implants – first centre in Poland and Central Europe

Permanent LDR brachytherapy and temporary HDR brachytherapy are competitive techniques for clinically localized prostate radiotherapy.

PDR – where are you?

Patients want to be cured by the least invasive method, those little risk of recurrence, lower risk of complications reported, and maintaining the high quality of life...

?

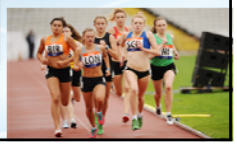
Difficult choices…

Prostatectomy:
*simple
*nerve sparing
*laparoscopic
*robot-assisted (Da Vinci)

External Beam:
* 3D
*IMRT
*Hypofractionation
*IGRT
*Tomotherapy
*Cyberknife
*Protons

Brachytherapy:
*LDR (seeds)
*HDR
*PDR
+/- hyperthermia

*HIFU
*Cryotherapy
*Nanoknife
*Hormonal therapy
*Chemotherapy
*Watchful Waiting
*Active Surveillance



We like to treat prostate cancer – why?

- High incidence,
- Easy to treat (location, size, shape…),
- Very good results – symposia highlights,
- Very good results – patient's satisfaction,
- Very good results – tribute for a hospital,
- Profitable method, money for a doctor,
- Interesting market for business…

USA disaster…

1. *Jeffrey M.* ***Martin****, Elizabeth A. Handorf, Alexander Kutikov, Robert G. Uzzo, Justin E. Bekelman, Eric M. Horwitz and Marc C. Smaldone. The rise and fall of prostate brachytherapy: Use of brachytherapy for the treatment of localized prostate cancer in the National Cancer Data Base.*

Cancer Article first published online : 15 APR 2014, DOI: 10.1002/cncr.28697

Aim: primary treatment trends focusing on the use of brachytherapy over time.

1. National Cancer Data Base (NCDB), a total of 1,547,941 patients with localized prostate cancer , from 1998 through 2010;
2. In the study cohort, brachytherapy use reached a peak of 16.7% in 2002, and then steadily declined to a low of 8% in 2010.
3. The most dramatic decline in BT was from academic centers - a decline of 48% compared to comprehensive community and community cancer centers.
4. Of the 719,789 patients with available data for risk stratification
   41.1%, 35.3%, and 23.6%, respectively, met low, intermediate, and high NCCN risk criteria.

(2002) 16,7 % ⇨ 8% (2010)

2. *Usama* ***Mahmood****, Thomas Pugh, Steven Frank, Lawrence Levy, Gary Walker, Waqar Haque, Matthew Koshy, William Graber, David Swanson, Karen Hoffman, Deborah Kuban1, Andrew Lee. Declining use of brachytherapy for the treatment of prostate cancer.*

Brachytherapy 13 (2014) 157-162

1. SEER database, where about 182,000 patients were treated between 2004-2009;
2. All BT used decreased from 44% in 2004 to 38% in 2009.

(2004) 44% ⇨ 38% (2009)

3. The difference in the utilization of EBRT monotherapy vs BT grew from 11.6% in 2004 to 24.0% in 2009.

USA disaster part II…

The reasons for a decline in BT usage are well discussed from both reports and includes:

1. **An increase in number of prostatectomies:**
   - 44% of treatment before the introduction of robotic prostatectomy in the early 2000s,
   - 60% of patients in 2010 (Martin et al.)

2. **Advances of EBRT such as IMRT, SBRT, and protons.**
   As discussed by Mahmood, a near complete transition from conventional EBRT to IMRT over the course of the past decade, from 0.15% in 2000 to 95.9% in 2008.

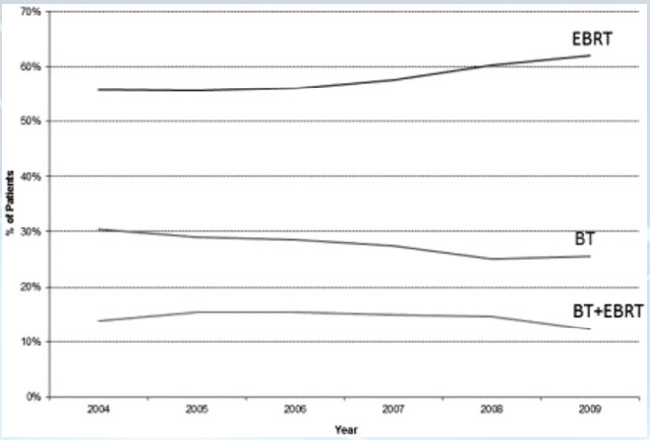
3. **Reimbursement with IMRT and the development of URORAD centers.**

4. **Negative press with the VA debacle of prostate BT.**

5. **Suboptimal volume of prostate BT procedures for current radiation oncology residents which is supportive by the declining use of BT in academic centers.**

Declining Use of Brachytherapy for the Treatment of Prostate Cancer

Usama Mahmood, Lawrence Levy, Gary Walker, Matthew Koshy, Thomas Pugh, Steven Frank, William Graber, Karen Hoffman, Deborah Kuban, Andrew Lee . Radiation Oncology, MD Anderson Cancer Center, Houston, TX; Radiation Oncology, University of Chicago, Chicago, IL; Urology, MD Anderson Cancer Center, Houston, TX.



2013
2013 ANNUAL MEETING
Quality Brachytherapy Through Education and Mentoring
April 18–20, 2013
Hyatt Regency, New Orleans, Louisiana

Patterns of care for brachytherapy in Europe: Updated results

Ferran Guedea, Jack Venselaar, Peter Hoskin, Taran Paulsen Hellebust, Didier Peiffert, Bradley Londres, Montse Ventura, Jean-Jacques Mazeron, Erik Van Limbergen, Richard Pötter, Gyorgy Kovacs

Radiotherapy and Oncology 97 (2010) 514–520

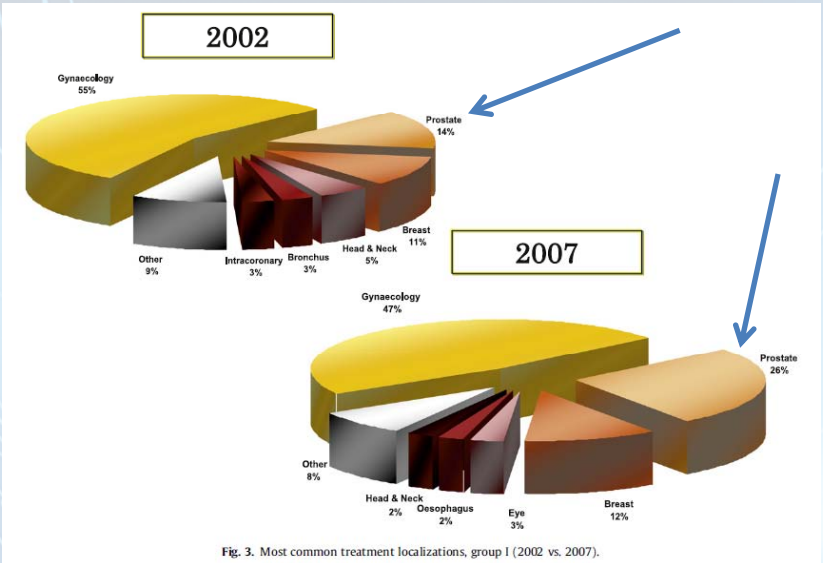
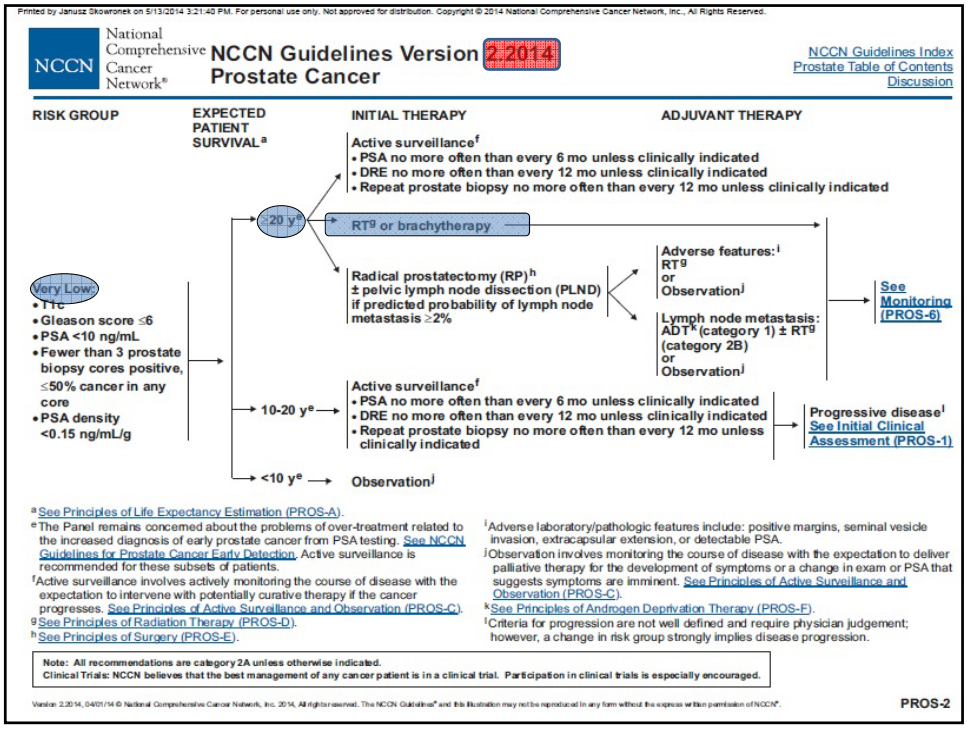


Fig. 3. Most common treatment localizations, group I (2002 vs. 2007).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Prostate Cancer
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Discussion
RISK GROUP
EXPECTED PATIENT SURVIVAL[a]
INITIAL THERAPY
ADJUVANT THERAPY
Active surveillance[f]
• PSA no more often than every 6 mo unless clinically indicated
• DRE no more often than every 12 mo unless clinically indicated
• Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
≥20 y[e]
RT[g] or brachytherapy
Radical prostatectomy (RP)[h] ± pelvic lymph node dissection (PLND) if predicted probability of lymph node metastasis ≥2%
Adverse features:[i] RT[g] or Observation[j]
Lymph node metastasis: ADT[k] (category 1) ± RT[g] (category 2B) or Observation[j]
See Monitoring (PROS-6)
Very Low:
• T1c
• Gleason score ≤6
• PSA <10 ng/mL
• Fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core
• PSA density <0.15 ng/mL/g
10-20 y[e]
Active surveillance[f]
• PSA no more often than every 6 mo unless clinically indicated
• DRE no more often than every 12 mo unless clinically indicated
• Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
Progressive disease[l] See Initial Clinical Assessment (PROS-1)
<10 y[e]
Observation[j]
[a] See Principles of Life Expectancy Estimation (PROS-A).
[e] The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.
[f] Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).
[g] See Principles of Radiation Therapy (PROS-D).
[h] See Principles of Surgery (PROS-E).
[i] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[j] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[k] See Principles of Androgen Deprivation Therapy (PROS-F).
[l] Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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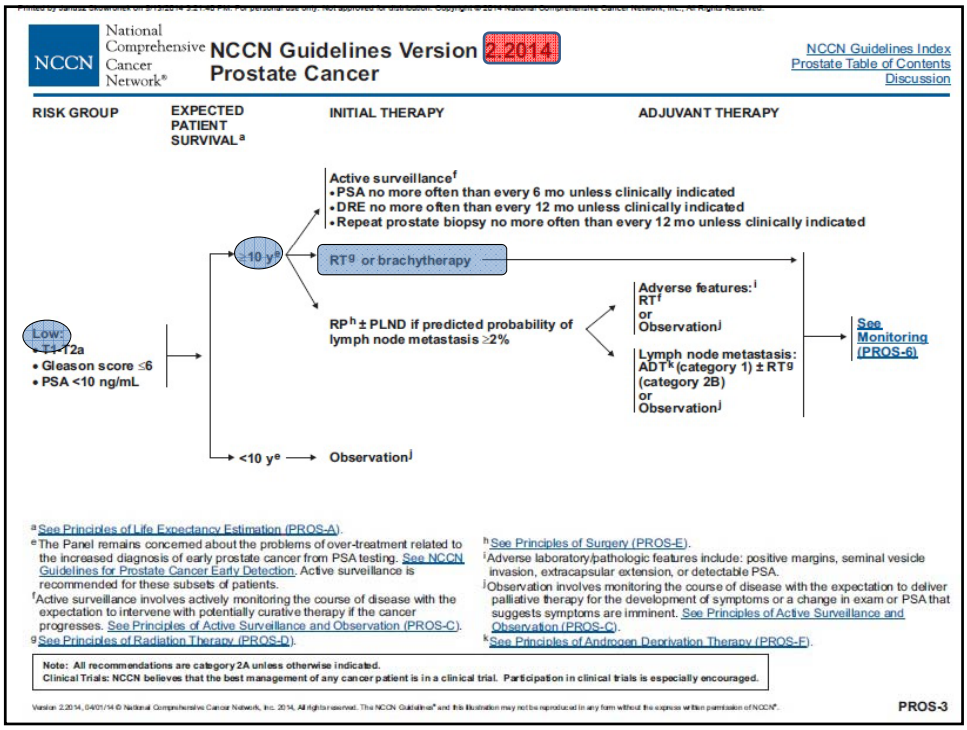
PROS-2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EXPECTED PATIENT SURVIVAL[a]
INITIAL THERAPY
ADJUVANT THERAPY
Active surveillance[f]
• PSA no more often than every 6 mo unless clinically indicated
• DRE no more often than every 12 mo unless clinically indicated
• Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
≥10 y[e]
RT[g] or brachytherapy
RP[h] ± PLND if predicted probability of lymph node metastasis ≥2%
Adverse features:[i] RT[g] or Observation[j]
Lymph node metastasis: ADT[k] (category 1) ± RT[g] (category 2B) or Observation[j]
See Monitoring (PROS-6)
Low:
• T1-T2a
• Gleason score ≤6
• PSA <10 ng/mL
<10 y[e]
Observation[j]
[a] See Principles of Life Expectancy Estimation (PROS-A).
[e] The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.
[f] Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).
[g] See Principles of Radiation Therapy (PROS-D).
[h] See Principles of Surgery (PROS-E).
[i] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[j] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[k] See Principles of Androgen Deprivation Therapy (PROS-F).
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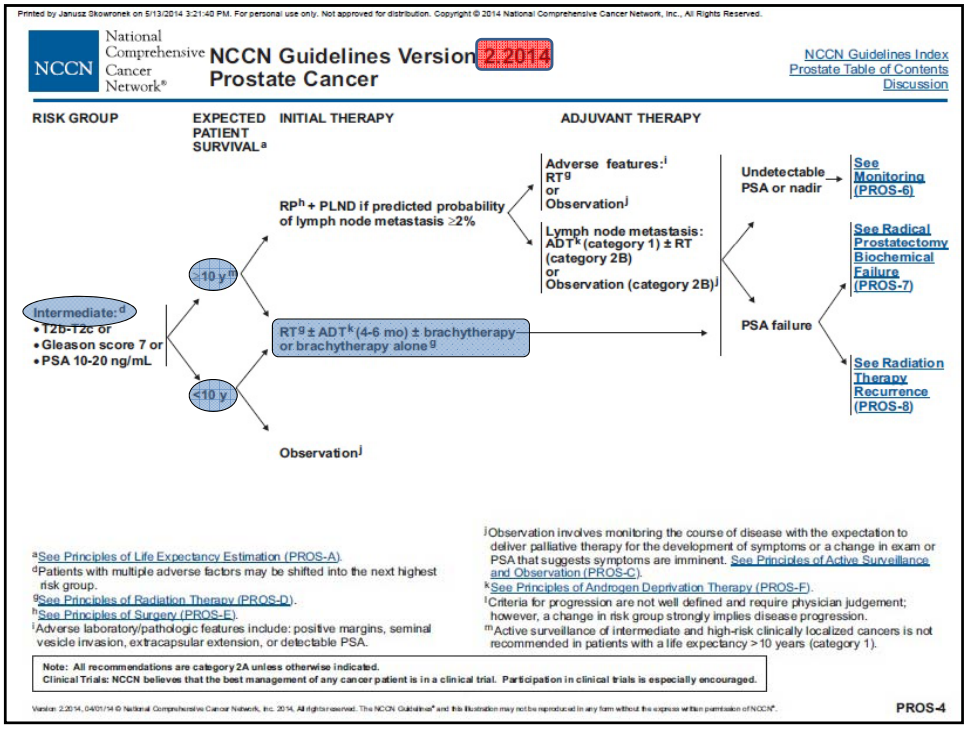
PROS-3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RISK GROUP
EXPECTED PATIENT SURVIVAL[a]
INITIAL THERAPY
ADJUVANT THERAPY
Intermediate:[d]
• T2b-T2c or
• Gleason score 7 or
• PSA 10-20 ng/mL
≥10 y[h]
<10 y
RP[h] + PLND if predicted probability of lymph node metastasis ≥2%
RT[g] ± ADT[k] (4-6 mo) ± brachytherapy or brachytherapy alone[g]
Observation[j]
Adverse features:[i] RT[g] or Observation[j]
Lymph node metastasis: ADT[k] (category 1) ± RT (category 2B) or Observation (category 2B)[j]
Undetectable PSA or nadir
See Monitoring (PROS-6)
PSA failure
See Radical Prostatectomy Biochemical Failure (PROS-7)
See Radiation Therapy Recurrence (PROS-8)
[a]See Principles of Life Expectancy Estimation (PROS-A).
[d]Patients with multiple adverse factors may be shifted into the next highest risk group.
[g]See Principles of Radiation Therapy (PROS-D).
[h]See Principles of Surgery (PROS-E).
[i]Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[j]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[k]See Principles of Androgen Deprivation Therapy (PROS-F).
[l]Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.
[m]Active surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).
Note: All recommendations are category 2A unless otherwise indicated.
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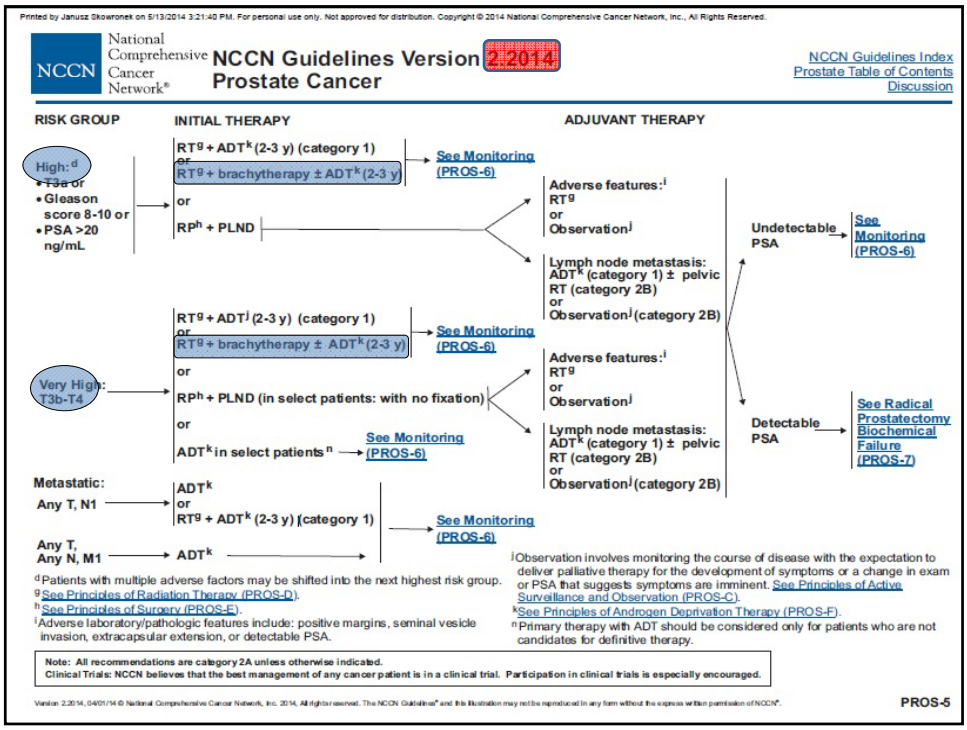
PROS-4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RISK GROUP
INITIAL THERAPY
ADJUVANT THERAPY
High:[d]
• T3a or
• Gleason score 8-10 or
• PSA >20 ng/mL
RT[g] + ADT[k] (2-3 y) (category 1) or RT[g] + brachytherapy ± ADT[k] (2-3 y)
See Monitoring (PROS-6)
or
RP[h] + PLND
Adverse features:[i] RT[g] or Observation[j]
Lymph node metastasis: ADT[k] (category 1) ± pelvic RT (category 2B) or Observation[j] (category 2B)
Undetectable PSA
See Monitoring (PROS-6)
RT[g] + ADT[j] (2-3 y) (category 1) or RT[g] + brachytherapy ± ADT[k] (2-3 y)
See Monitoring (PROS-6)
Very High: T3b-T4
or
RP[h] + PLND (in select patients: with no fixation)
Adverse features:[i] RT[g] or Observation[j]
Lymph node metastasis: ADT[k] (category 1) ± pelvic RT (category 2B) or Observation[j] (category 2B)
Detectable PSA
See Radical Prostatectomy Biochemical Failure (PROS-7)
or
ADT[k] in select patients[n]
See Monitoring (PROS-6)
Metastatic:
Any T, N1
ADT[k] or RT[g] + ADT[k] (2-3 y) (category 1)
See Monitoring (PROS-6)
Any T, Any N, M1
ADT[k]
[d]Patients with multiple adverse factors may be shifted into the next highest risk group.
[g]See Principles of Radiation Therapy (PROS-D).
[h]See Principles of Surgery (PROS-E).
[i]Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[j]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[k]See Principles of Androgen Deprivation Therapy (PROS-F).
[n]Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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PROS-5

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RADIATION THERAPY RECURRENCE

Biochemical failure[p] or Positive DRE

Candidate for local therapy:
- Original clinical stage T1-T2, NX or N0
- Life expectancy >10 y
- PSA now <10 ng/mL

- PSADT
- TRUS biopsy
- Bone scan[b]
- ± Abdominal/pelvic CT/MRI[b]
- Prostate MRI[b]
- ± C-11 choline PET[b]

TRUS biopsy positive, studies negative for distant metastases → Observation[j] or RP[h] or Cryosurgery or Brachytherapy[g]

TRUS biopsy negative, studies negative for distant metastases → Observation[j] or ADT[k] or Clinical trial or More aggressive workup for local recurrence (eg, repeat biopsy, MR spectroscopy, Prostate MRI) → Progression → See Advanced Disease (PROS-9)

Studies positive for distant metastases → ADT[k] or Observation[j]

Not a candidate for local therapy → ADT[k] or Observation[j]

[b] See Principles of Imaging (PROS-B).
[g] See Principles of Radiation Therapy (PROS-D).
[h] See Principles of Surgery (PROS-E).
[j] Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent See Principles of Active Surveillance and Observation (PROS-C).
[k] See Principles of Androgen Deprivation Therapy (PROS-F).
[p] RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - 1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.

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PRINCIPLES OF RADIATION THERAPY

Primary EBRT:
- 3-D conformal RT or IMRT techniques should be used to treat prostate cancer. IGRT is required if dose is ≥ 78 Gy. IMRT, if available, is preferred.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2 to 3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4 to 6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques of IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Treatment results appear better when disease burden is lower. Radiation should be administered before PSA exceeds 0.5 ng/mL.

Primary/Salvage Brachytherapy:
- Permanent low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, consider combining brachytherapy with EBRT (40-50 Gy) ± 4 to 6 mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 4 to 6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

Continued on next page

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PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy (EBRT)

- Highly conformal RT techniques should be used to treat prostate cancer.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Moderately hypofractionated image-guided IMRT regimens (2.4 to 4 Gy per fraction over 4-6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2 to 3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4- to 6-mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques of IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.

Primary/Salvage Brachytherapy

- Permanent low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, consider combining brachytherapy with EBRT (40-50 Gy) ± 4- to 6-mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 2 to3 y-neoadjuvant/concomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from ADT and prostate size may not decline.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used alone or in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy x 2 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

Note: All recommendations are category 2A unless otherwise indicated.
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Continued on next page

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Brachytherapy

Brachytherapy is used traditionally for low-risk cases since earlier studies found it less effective than EBRT for high-risk disease.[6,124] However, increasing evidence suggests that technical advancements in brachytherapy may provide a role for contemporary brachytherapy in high-risk localized and locally advanced prostate cancer.[125] Brachytherapy involves placing radioactive sources into the prostate tissue. There are currently two methods for prostate brachytherapy: low dose-rate (LDR) and high dose-rate (HDR).

LDR Brachytherapy

LDR brachytherapy consists of placement of permanent seed implants in the prostate. The short range of the radiation emitted from these low-energy sources allows delivery of adequate dose levels to the cancer within the prostate, whereas excessive irradiation of the bladder and rectum can be avoided. Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution.

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to radical prostatectomy (over 90%) for low-risk tumors with medium-term follow-up.[126] In addition, the risk of incontinence is minimal in patients without a previous transurethral resection of the prostate (TURP), and erectile function is preserved in the short term.[109] Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention. Irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is greater after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years. IMRT causes less acute and late genitourinary toxicity and similar freedom from biochemical failure compared with iodine-125 or palladium-103 permanent seed implants.[127,128]

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers (cT1c–T2a, Gleason grade 2-6, PSA <10 ng/mL). For intermediate-risk cancers, brachytherapy may be combined with EBRT (45 Gy) with or without neoadjuvant ADT, but the complication rate increases.[129,130] Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy.

Patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP are not ideal candidates for brachytherapy. For these patients, implantation may be more difficult and there is an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size, however, increased toxicity would be expected from ADT and prostate size may not decline. Post-implant dosimetry should be performed to document the quality of the implant.[131] The recommended prescribed doses for monotherapy are 145 Gy for iodine-125 and 125 Gy for palladium-103.

HDR Brachytherapy

HDR brachytherapy, which involves temporary insertion of a radiation source, is a newer approach that provides a "boost" dose in addition to EBRT for patients at high risk of recurrence. Combining EBRT (40-50 Gy) and HDR brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.[132-135] Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT.[136-138] An analysis of a cohort of 12,745 high-risk patients found that treatment with brachytherapy (HR, 0.66; 95% CI, 0.49-0.86) or brachytherapy plus EBRT (HR, 0.77; 95% CI, 0.66-0.90) lowered disease-specific mortality

compared to EBRT alone.[139] Common boost doses include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, or 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy x 2 fractions.

Addition of ADT (2 or 3 years) to brachytherapy and EBRT is common for patients at high risk of recurrence. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-specific survival reaching 87% and 91%, respectively.[140,141] However, it remains unclear whether the ADT component contributes to outcome improvement. D'Amico and colleagues studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease.[142] Addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. The use of all three modalities reduced prostate cancer-specific mortality compared to brachytherapy alone (adjusted HR, 0.32; 95% CI, 0.14-0.73). Other analyses did not find an improvement in failure rate when ADT was added to brachytherapy and EBRT.[143,144]

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).[145,146] Vargas and colleagues[147] reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

Proton Therapy

Proton beams can be used as an alternative radiation source.[148] The costs associated with proton beam facility construction and proton beam treatment are high.[149] Two comparisons between men treated with proton beam therapy and EBRT show similar early toxicity rates.[149,150] A single-center report of prospectively collected quality-of-life data 3 months, 12 months, and >2 years after treatment revealed significant problems with incontinence, bowel dysfunction, and impotence.[150] Perhaps most concerning is that only 28% of men with normal erectile function maintained normal erectile function after therapy.

The NCCN panel echoed the following statement by ASTRO in its review of proton beam therapy: "Prostate cancer has the most patients treated with conformal proton therapy of any other disease site. The outcome is similar to IMRT therapy, however, with no clear advantage from clinical data for either technique in disease control or prevention of late toxicity. This is a site where further head-to-head clinical trials may be needed to determine the role of proton beam therapy. In addition, careful attention must be paid to the role of dosimetric issues including correction for organ motion in this disease. Based on current data, proton therapy is an option for prostate cancer, but no clear benefit over the existing therapy of IMRT photons has been demonstrated."[151]

Radiation for Metastases

Radiation is an effective means of palliating bone metastases from prostate cancer. In May 2013, the Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic castration-recurrent prostate cancer (CRPC) in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase III, randomized trial including 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.[152] Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved overall survival (median 14.9 months vs. 11.3 months; HR,

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Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 4, pp. 789–799, 1999

0360-3016/99/$–see front matter

PII S0360-3016(99)00069-3

CLINICAL INVESTIGATION **Prostate**

AMERICAN BRACHYTHERAPY SOCIETY (ABS) RECOMMENDATIONS FOR TRANSPERINEAL PERMANENT BRACHYTHERAPY OF PROSTATE CANCER

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BRACHYTHERAPY

Brachytherapy 6 (2007) 34–37

American Brachytherapy Society recommends no change for prostate permanent implant dose prescriptions using iodine-125 or palladium-103

Mark J. Rivard[1,*], Wayne M. Butler[2], Phillip M. Devlin[3], John K. Hayes Jr.[4], Robert A. Hearn[5], Eugene P. Lief[6], Ali S. Meigooni[7], Gregory S. Merrick[2], Jeffrey F. Williamson[8]

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BRACHYTHERAPY

Brachytherapy 11 (2012) 6–19

American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy

Brian J. Davis[1,*], Eric M. Horwitz[2], W. Robert Lee[3], Juanita M. Crook[4], Richard G. Stock[5], Gregory S. Merrick[6], Wayne M. Butler[6], Peter D. Grimm[7], Nelson N. Stone[8], Louis Potters[9], Anthony L. Zietman[10], Michael J. Zelefsky[11]

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 2, pp. 335–341, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.045

ASTRO GUIDELINE

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE TRANSPERINEAL PERMANENT BRACHYTHERAPY OF PROSTATE CANCER

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ELSEVIER

Radiotherapy and Oncology 57 (2000) 315–321

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

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ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer

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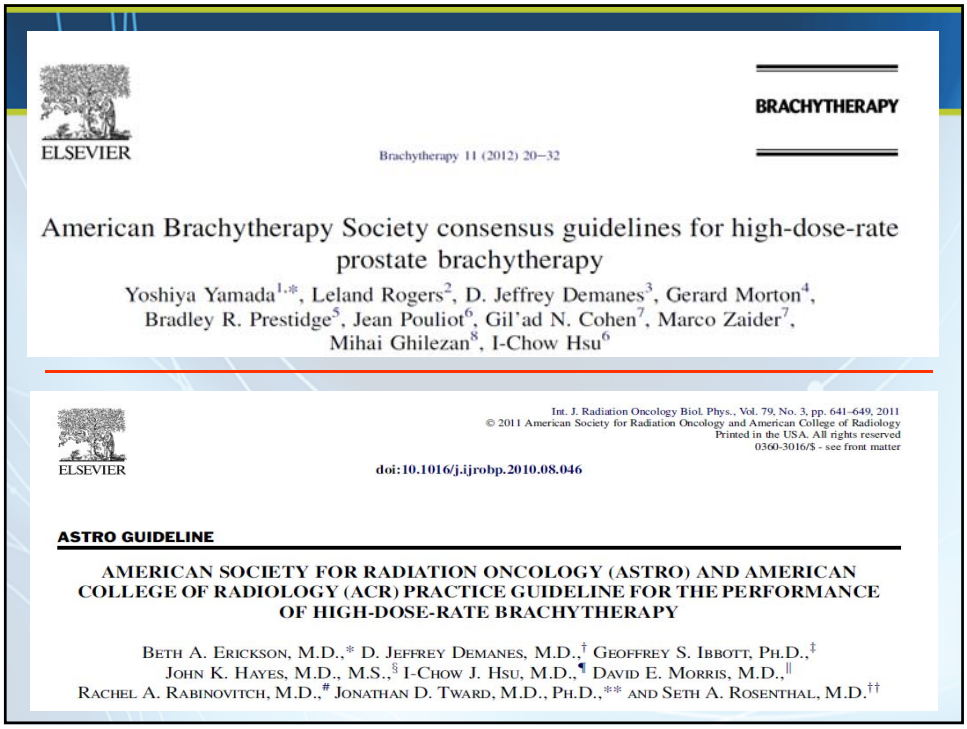
Received 18 September 2000; accepted 27 September 2000



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BRACHYTHERAPY

Brachytherapy 11 (2012) 20–32

American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

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ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 641–649, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.08.046

ASTRO GUIDELINE

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF HIGH-DOSE-RATE BRACHYTHERAPY

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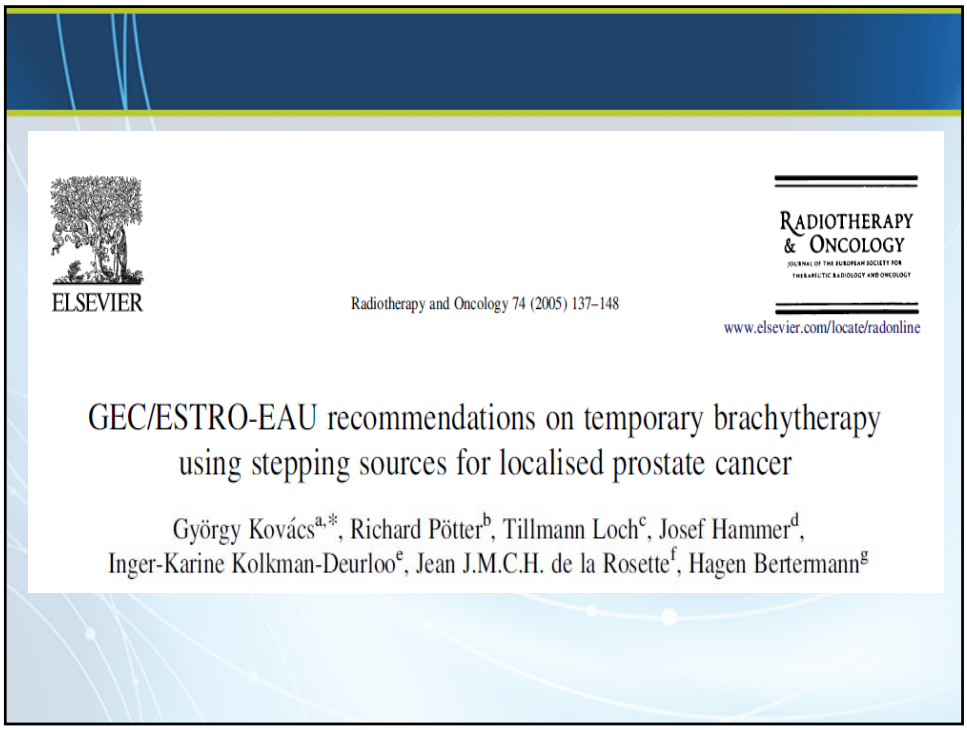

ELSEVIER

Radiotherapy and Oncology 74 (2005) 137–148

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer

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August, 2008

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ABS PROSTATE HIGH-DOSE RATE TASK GROUP *I-Chow Hsu, MD, Yoshiya Yamada MD, Eric Vigneault MD, Jean Pouliot, PhD August, 2008*	ABS PROSTATE LOW-DOSE RATE TASK GROUP *Gregory S. Merrick, M.D., Michael J. Zelefsky, M.D., John Sylvester, M.D., Subir Nag, M.D., William Bice, Ph.D.*	GEC-ESTRO – High-Dose-Rate *Gyorgy Kovacs, Richard Pötter, Tillmann Loch, Josef Hammer, Inger-Karine Kolkman-Deurloo, Jean J.M.C.H. de la Rosette, Hagen Bertermann, 2005*
Inclusion Criteria:		
Clinical Stage:		
T1-T3b and selected T4	T1b-T2c and selected T3	T1b–T3b
Gleason Score:		
Gleason score 2-10	Gleason scores 2-10	Any Gleason score
PSA:		
No upper limit, but in almost all cases, patient does not have documented distant metastasis (TxN0M0)	In almost all cases, a PSA≤ 50 ng/mL	Any iPSA without distant metastases
	No pathologic evidence of pelvic lymph node involvement No distant metastases	

ABS PROSTATE HIGH-DOSE RATE TASK GROUP	ABS PROSTATE LOW-DOSE RATE TASK GROUP	GEC-ESTRO High -Dose-Rate, Low-Dose-Rate
Patient Selection Criteria:		
Monotherapy:		
Clinical T1b-T2b and Gleason score ≤ 7 and PSA ≤ 10 ng/mL	• Clinical stage T1b-T2b and Gleason score ≤ 6 and PSA ≤ 10 ng/mL • Select higher risk patients • Salvage of select radiation therapy failures	• Clinical stage T1b-T2a • iPSA< 10 ng/ml, • Gleason max. 6
Boost:		
• Patients with high risk features such as T3-T4, Gleason score 7-10, and/or PSA > 10 ng/mL • Selected patients with "bulky" T1-2b tumor (inadequate information exists to clearly define bulky tumor based on DRE, TRUS, percentage positive biopsies)	≥ clinical stage T2c and/or Gleason score ≥ 7 and/or PSA > 10 ng/mL	Stages T1b–T3b Any Gleason score Any iPSA without distant metastases
	Special clinical situations: Inadequate information exists to recommend supplemental XRT based on perineural invasion, percent positive biopsies and/or MRI-detected extracapsular penetration	

ABS PROSTATE HIGH-DOSE RATE TASK GROUP	ABS PROSTATE LOW-DOSE RATE TASK GROUP	GEC-ESTRO – High -Dose-Rate, Low-Dose-Rate	ABS consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy *Davis BJ et al.*
Exclusion Criteria:			
Relative Contraindications:			
• Severe urinary obstructive symptoms • Extensive TURP defect or TURP within 6 month • Collagen vascular disease	• Severe urinary irritative/obstructive symptomatology • Extensive TURP defect • Substantial median lobe hyperplasia • Prostate dimensions larger than the grid (i.e., > 60 mm in width and > 50 mm in height) • Severe pubic arch interference • Gross seminal vesicle involvement • Prior pelvic radiotherapy • Inflammatory bowel disease • Pathologic involvement of pelvic lymph nodes	•Volume > 60 cm3 •TURP within 6 months •Infiltration of the external sphincter of the bladder neck •Significant urinary obstructive symptoms •Pubic arch interference •Rectum-prostate distance on TRUS < 5 mm	• High IPSS (typically defined as > 20) • History of prior pelvic radiotherapy • Transurethral resection defects • Large median lobes • Gland size < 60 cm3 at time of implantation • Inflammatory bowel disease
Absolute Contraindications:			
• Unable to undergo anesthesia (general, spinal, epidural, or local) • Unable to lay flat	• Distant metastases • Life expectancy < 5 years		• Limited life expectancy • Unacceptable operative risks • Distant metastases • Large TURP defects, which preclude seed placement and acceptable radiation dosimetry • Ataxia telangiectasia

ABS PROSTATE HIGH-DOSE RATE TASK GROUP	ABS PROSTATE LOW-DOSE RATE TASK GROUP and ESTRO/EAU/EORTC Low-Dose Rate	ABS consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy *Davis BJ et al.*
Doses		
Monotherapy		
10.5 Gy x 3 8.5-9.5 Gy x 4 6.0-7.5 Gy x 6	Pd-103 125 Gy (110-120 Gy) I-125 145 Gy (140-160 Gy) Cs-131 115 Gy	Pd-103 110-125 Gy I-125 140-160 Gy
BT + EBRT		
15 Gy x 1 (with 36-40 Gy XRT) 9.5-10.5 Gy x 2 (with 40-50 Gy XRT) 5.5-7.5 Gy x 3 (with 40-50 Gy XRT) 4.0-6.0 Gy x 4 (with 36-50 Gy XRT)	Pd-103 Boost (with 41.4 – 50.4 Gy EBRT) 90-100 Gy I-125 Boost (with 41.4 – 50.4 Gy EBRT) 108-110 Gy	Pd-103 Boost (with 41.4 – 50.4 Gy EBRT), 1,8 – 2,0 Gy/fr. 90-100 Gy I-125 Boost (with 41.4 – 50.4 Gy EBRT), 1,8 – 2,0 Gy/fr. 108-110 Gy

ABS PROSTATE HIGH-DOSE RATE TASK GROUP	ABS PROSTATE LOW-DOSE RATE TASK GROUP
PTV	
The definition of volumes will be in accordance with ICRU Report 58: Dose and Volume Specification for reporting interstitial therapy. • Clinical Target Volume (CTV) is defined by the physician on the treatment planning scan. • For T1c-T2b, the brachytherapy CTV includes the prostate only • For T3a-T3b, the brachytherapy CTV includes the prostate and extra-capsular extension. • PTV = CTV.	• Prostate with margin • Seminal vesicles • Prostate minus non-cancerous regions of the gland (e.g., anterior base) • Image-guided target volumes such as indium-111 or MR spectroscopy

ABS PROSTATE HIGH-DOSE RATE TASK GROUP	ABS PROSTATE LOW-DOSE RATE TASK GROUP	ABS consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy *Davis BJ et al..*	GEC-ESTRO/EAU - High-Dose-Rate	ESTRO/EAU/EORTC Low-Dose-Rate *Daniel Ash, Anthony Flynn, Jan Battermann, Theodorous de Reijke, Paulo Lavagnini, Leo Blank*
Recommended evaluated postoperative dosimetric parameters:				
• The prescription dose will be given only to the PTV. • The goal is to deliver the prescription dose to at least 90% of the PTV (V100 prostate >90%). • The volume of bladder and rectum receiving 75% of the prescription dose should be kept to less than 1 cm^3 (V_{75} rectum and V_{75} bladder < 1 cm^3) • the volume of urethra receiving 125% of the prescription dose should be kept to less than 1 cm^3 (V_{125} urethra < 1 cm^3).	• V_{100} • V_{150} • V_{200} • D_{90} • Urethral doses - should include: UV_{125}, UV_{150}, UD_{50}, UD_{30}, UD_5 and/or maximum and minimum dose • Rectal doses - cubic centimeters of rectum which received ≥ prescription dose (RV_{100})	• Prostate: • D90 (in Gy and percent) • V100 and V150 (in percent) • Urethra: UV150 (in volume) • UV5, UV30 (percent) • Rectum: • RV100 (in volume)	• Dose rate and dose per fraction of the target dose • (D100, D90) for CTV 1, CTV 2 and CTV 3 • Number and duration of the fractions • Time interval between fractions and the overall time	• The volume implanted • The number of seeds • The number of needles used • The total activity implanted • The prescribed dose • The D90, that is the dose that covers 90% of the prostate volume as defined from post implant imaging • The V100, that is the percentage of the prostate volume that has received the prescribed dose • V150, the volume that has received 50% more than the prescribed dose

Yamada et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy 2012; 11: 20-32

Current dose fractionation schedules

Institution	Dose Fractionation	Bladder	Urethra	Rectum
MSKCC	Boost 7 Gy x 3 Mono 9.5 Gy x 4 Salvage 8 Gy x 4		< 120% prescription	$D2_{cc}$<70%
UCSF	Boost 15 Gy x 1 Mono 10.5 Gy x 3 Salvage 8 Gy x 4*	V_{75}<1 $_{cc}$	V_{125}<1 $_{cc}$, V_{150} = 0 $_{cc}$ *(dose tunnel whenever possible)	V_{75}<1 $_{cc}$
WBH	Boost 10.5 Gy x 2 Mono 4 x 9.5 Gy (historical) 12-13.5 Gy x 2 (current) Salvage 7 Gy x 4 combined with hyperthermia	No constraint (intra-op TRUS-based dosi)	V_{100}< 90% of prescription V_{115} < 1% of prescription	V_{75} < 1% of prescription
TCC	Boost 6 Gy x 2 2 implants	< 80% of Rx	< 125% of prescription	< 80% of Rx to outer wall
GW	Boost 6.5 Gy x 3 Mono two sessions of 6.5 Gy x 3	< 100% prescription	< 110% prescription	mucosa < 60%, outer wall < 100%
Toronto	Boost 15 Gy x 1	n/a	D_{10} < 118% Max < 125%	V80 < 0.5 cc
UCLA-CET	Boost 6 Gy x 4 Mono 7.25 Gy x 6	90 - 100% wall 80% balloon	120% combo 105% any TUR 110% mono	Rectal wall 80% Rectal wall 80 - 85%

MSKCC5Memorial Sloan-Kettering Cancer Center; UCSF5University of California San Francisco;WBH5William Beaumont Hospital; TCC5Texas Cancer Center;GW5GammaWest Brachytherapy; Toronto5University of Toronto; UCLA-CET5University of California Los Angeles-California Endocurietherapy Cancer Center; V805fractional volume covered by 80% of the prescription dose; V1005fractional volume covered by 100% of the prescription dose; V1155fractional volume covered by 100% of the prescription dose; V1255fractional volume covered by 125% of the prescription dose; V1505fractional volume covered by 150% of the prescription dose; D105dose that covers the highest 10% of the organ; Rx5prescription; TUR5transurethral resection

HDR & LDR & PDR Brachytherapy: Diagnostics, Equipment, Personnel – the same

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Team

Experience in:

1. TRUS (done by radiotherapist, urologist?),
2. Dosimetry, treatment planning,
3. Needles (seeds) implantation (radiotherapist),
4. Radiotherapy knowledge.

Team:

1. radiation oncologist,
2. urologist, radiologist or radiation oncologist with US skills,
3. physicist,
4. 2-3 nurses,
5. anesthetist,
6. nurse anesthetic,
7. X-ray technician.

PDR

?

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PDR

EBRT + PDR

Author	N=	EBRT	PDR	Follow-up	Results	Complications
Geiger MH et al. (Erlangen), 2005	91	T1-2 45 Gy T3 – 50,4 Gy	25 Gy (0,6 Gy/h) – 26 pts 30 Gy (0,65 Gy/h) – 59 pts	18 months	9% - recurrence	11% - urinary
Pieters B et al. (Amsterdam), 2005	27	46 Gy	29 Gy (1,0 Gy/h)	3 months		Low toxicity – 17,4% GU in 12 week
Izard MA et al. (IJORB 2006)	165	50,4 Gy	18 Gy in 3 fractions (6h interval), 0,5-1,0 Gy/h	36 months	98% - CSS 93% - OS	
Lettmaier S et al. (RO 2012)	130	50,4 Gy	25 Gy – 33 pts 30 Gy – 63 pts 35 Gy – 34 pts (1 session, 0,6-0,7 Gy.1h/24 pulses	60 months	85,6% - DFS	15% - GI 1/2 grade 15% - GU 1/2 grade
Pieters B et al. (IJORB 2011)	110	46 Gy	24,96-28.80 Gy	60 months	99% - 3 yrs 96% - 5 yrs	12% - GI grade 2 26,9% - GU grade 2

PDR

PDR monotherapy					
Author	**N=**	**PDR**	**Follow-up**	**Results**	**Complications**
Geiger MH et al. (Erlangen), 2005	16	65 Gy in 2 fractions, 0,65 Gy/h/24 pulses	(12 months)		0%
Lahmer G et al. (Strahl Oncol 2013	18 - recurrence	30 Gy, 2 fractions (0,6 Gy/h/24 pilses)	36 months	88,9 % - OS 57,1 % - PSA RFS	11,1 % GU 2 16,7 % GU 3

PDR - Erlangen schedules

- T1-2cN0M0, PSA < 10, Gleason < 7, V < 60 cm3
  – sole PDR, 2 x 35 Gy, 0.70 Gy/h
- T2b-c N0M0, PSA < 10, Gleason < 7, V < 60 cm3
  – EBRT 50.4 Gy and PDR „boost" 35 Gy, 0.70 Gy/h
- T3, PSA ≤ 10, Gleason < 7, V < 60 cm3
  – EBRT 50.4 Gy, hormonal therapy and PDR „boost" 35 Gy, 0.70 Gy/h

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Seeds LDR brachytherapy - Advantages over HDR

- Large worldwide clinical experience and long-term data available,
- Patient and Doctor convenience,
- One-day patient turnover,
- Ideal for patients with pre-existing comorbidities precluding prolonged hospitalization,
- Ideal for patients with AUA scores of ≤12.

Seeds LDR brachytherapy - Disadvantages over HDR

- Dosimetric uncertainties regarding final seeds distribution and dosimetry (gland swelling, seeds migration, clumping),
- No accurate post-implant plan in the OR since individual seed position identification is not yet possible,
- Dosimetry (CT) is performed after patient leaves the OR,
- Real implant dosimetry varies with time from procedure ("cold implants" until prostate edema subsides, seeds migration/clumping may add to dose inhomogeneity over effective treatment time (6 months for I-125).

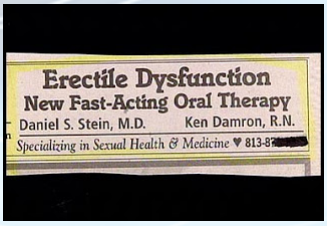
Seeds LDR brachytherapy - Disadvantages over HDR

- Operator-dependent and patient volume-dependent to maintain expertise
- Longer resolution of urinary symptoms

Acute urinary toxicity

Seeds LDR brachytherapy - Disadvantages over HDR

- Less likely to preserve erectile function



Seeds

Sole LDR brachytherapy:

Advantages

- good treatment results (similar to surgery)
- relatively small rate of complications
- short treatment time (1-3 days)

Disadvantage

- in the past – seed migration possibility
- small risk of relatives irradiation
- costs

HDR

Advantages

- good treatment results (similar to seeds)
- possibility of dose verifacion
- complications similar to
- positive radiobiology
- no staff exposure to radiation

Disadvantage

- different fractionation schemas
- in monotherapy – small trial's number

HDR

Advantages

1. Radiation protection:
- HDR eliminates radiation exposure hazard for care givers and visitors
- eliminates source preparation and transportation
- is minimal risk of losing a radioactive source

2. Allows shorter treatment times:
- less patient discomfort
- to treat patients who may not tolerate long periods of isolation
- less risk of applicator movement
- reduced hospitalization costs
- possible to treat a larger number of patients

3. HDR sources are of smaller diameter than the other sources:
- allows for interstitial, intraluminal, and percutaneous insertions.

4. HDR makes treatment dose distribution optimization possible:
- variations of the dwell times of a single stepping source and the source position

Disadvantages

1. Radiobiological:
- The short treatment times do not allow for the repair of sublethal damage in normal tissue or the redistribution of cells within the cell cycle or reoxygenation

2. Limited experience:
- In US

3. The economic disadvantage:
- a large initial capital expenditure since the remote afterloaders cost
- additional costs for a shielded room and personnel costs are higher

4. Greater potential risks:
- greater potential harm if the machine malfunctions or if there is a calculation error.
- the short treatment times, compared to LDR, allow much less time to detect and correct errors.

Conclusions

At present, the available clinical data with these two techniques

suggests

that they are equally effective,

stage for stage,

in providing high tumor control rates.

Conclusions

Easily money can decide on the treatment of patients and not the curability or quality of life after treatment.

Our choice…


Thank you
Journal of Contemporary BRACHYTHERAPY