NEW Technology to diagnose, target and treat PROSTATE CANCER

US Too International – 20th Annual Symposium
Chicago – August 20-21, 2010
Michael Dattoli, MD
It has been an **Evolution**

- Suspecting prostate cancer
- Detecting abnormal tissue
- Locating tumor sites
- Biopsying active cells
- Diagnosing Gleason, aggressiveness
- Evaluating local vs distant disease spread (stage)
- Determining most effective treatment
- Accomplishing that treatment
Basic Categories of Treatment

• Old “Gold Standard” surgery
  – Open; laparoscopic vs robotic
• Radiation
  – External; internal; combination
• Freezing
• Heating
• HIFU
• Biothermy
• Hormonal therapy
• Watching waiting/Expectant surveillance
Recurrent Prostate Cancer
Who is most at risk?

Current NCCN Staging Guidelines

<table>
<thead>
<tr>
<th>Pre-treatment Risk Categories</th>
<th>% 5-yr Failure Rate Following Treatment</th>
</tr>
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<tbody>
<tr>
<td>Low Risk: Stage $\leq T_{2a}$, or Gleason $\leq 6$, or PSA $\leq 10$</td>
<td>25%</td>
</tr>
<tr>
<td>Intermediate Risk: Stage $T_{2b} - T_{2c}$, or Gleason 7, or PSA 10-20</td>
<td>$\leq 50%$</td>
</tr>
<tr>
<td>High Risk: Stage $\geq T_{3a}$, or Gleason 8-10, or PSA $&gt; 20$</td>
<td>$&gt;50%$</td>
</tr>
</tbody>
</table>
Risk Factors for Prostate Cancer Recurrence

Where are YOU within these risk categories?
Do you know?
Should you be concerned?
Over 3 million American men are survivors of prostate cancer and the number is growing every day!
What about Watchful Waiting?

...Problems with Watchful Waiting

Supportive data based on older flawed European studies

More recent data including:

1) 2003 UCSF/CAPSURE trial (watchful waiting Vs prostatectomy >10,000 patients) closed after only 5 years due to adverse findings, i.e. 72% of watchful waiting patients required Androgen deprivation

2) 2006 Medicare SEER data (U.S. study of men ages 65-80) found very statistically significant benefit to treatment (radiation or surgery)

3) 2008 Lancet Oncology Study, found prostate cancer mortality in the U.S. to improve over 4-fold since 1994 when compared to men in the U.K. (while the mortality declined and was sustained in U.S. patients aged 75 and older.

4) 2010 European study (follow up 14 years) demonstrated 27% decrease in death rate with screening and treatment compared to non screening group.
And how about the whole screening question?

1. 2010 Lancet Oncology article, reported PSA screening in men ages 50-69 reduced prostate cancer deaths by 50%.

2. Science Daily July 2010, Baseline PSA Predicts Risk of Death from Prostate Cancer. Men who have a baseline PSA value of 10 or higher the first time they are tested are up to 11 times more likely to die from prostate cancer than are men with lower initial values, and Duke University researchers say this study supports the advantages of routine, early PSA testing.
# Projected Expectancy of Life: United States, (Men)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>23.53</td>
<td>22.5 years</td>
</tr>
<tr>
<td>65</td>
<td>19.49</td>
<td>18.7</td>
</tr>
<tr>
<td>70</td>
<td>15.69</td>
<td>15.1</td>
</tr>
<tr>
<td>75</td>
<td>12.24</td>
<td>11.9</td>
</tr>
<tr>
<td>80</td>
<td>9.16</td>
<td>9.1</td>
</tr>
<tr>
<td>85</td>
<td>6.1</td>
<td>6.8</td>
</tr>
<tr>
<td>90</td>
<td>4.52</td>
<td>5.0</td>
</tr>
<tr>
<td>95</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>100</td>
<td>2.29</td>
<td>2.6</td>
</tr>
</tbody>
</table>
The Big Challenge

Location, location, location!
Just where is the tumor?
Where does it start?
Where does it end?
Where is the capsule?
Paramedian (sagittal) dissection

- External iliac vessels
- Peritoneum
- Rectus abdominis muscle
- Anterior layer of rectus sheath
- Transversalis fascia
- Umbilical prevesical fascia
- Subcutaneous tissue
  - fatty (Camper’s)
  - membranous (Scarpa’s)
- Superior pubic ramus (cut)
- Fundiform ligament of penis
- Suspensory ligament of penis
- Areolar tissue and vesical venous plexus in retro-pubic (prevesical) space
- Deep dorsal vein of penis
- Corpus cavernosum
- Deep (Buck’s) fascia of penis
- Corpus spongiosum
- Superficial (dartos) fascia of penis and scrotum
- Septum of scrotum
- Ischiocavernous muscle
- Testis

Ductus (vas) deferens
- Urinary bladder and fascia
- Ureter (cut)
- Seminal vesicle
- Rectovesical pouch
- Rectum
- Rectoprostatic (Denonvilliers’) fascia
- Prostate (covered by fascia)
- Ischiopubic ramus (cut)
- Pelvic diaphragm (levator ani muscle)
- Deep transverse perineal muscle
- Perineal body

Deep
- Superficial
  - External anal sphincter muscle
- Subcutaneous
- Deep perineal (investing or Gallaudet’s) fascia
- Superficial perineal (Colles’) fascia
  - (interior fascia of superficial perineal space)
- Superficial (dartos) fascia of scrotum
- External spermatic fascia

location, location, location
Vascularure and Innervation

- Pelvic plexus
- Ureter
- Ductus deferens
- Urinary bladder
- Umbilical a.
- Pubic symphysis
- Deep dorsal vein of the penis
- Prostatic plexus
- Prostate gland
- Inferior vesical a., v.
- Middle vesical a., v.
- Vesical plexus
- Urogenital diaphragm

location, location, location
location, location, location!

**FIGURE 4.** MRI of prostate with 3TP software overlay showing contrast kinetics with matching whole mount specimen from a radical prostatectomy. There is excellent correlation between the red areas indicating areas of high contrast inflow and washout consistent with cancer in the peripheral zone and the whole mount specimen, where the cancer is circled in red. (Provided by 3TP)

DCE- MRI

*Show me the capsule!*
Suppose this is a cancer -
Cancers really look like this -
Suppose this is your prostate -
And this is your prostate with a cancer-
But this is *really* what it looks like -
What Works (and why not)

• Problems with Surgery
  – Invasive, bloody, risk of infection, prolonged recovery
  – *Always* some prostate tissue is left
  – Collateral damage to surrounding tissue and organs – side effects!
  – Does not address “fingers”
Suppose your prostate has been removed.
This may be what the region looks like following prostatectomy-
The “Perfect Treatment”

The PERFECT Treatment for the PERFECT Patient in a PERFECT World

% Cancer-Free

Time in Years >
Recurrence after Prostatectomy

How common in contemporary times?
Prostatectomy Vs Radiation
Show Me the Data!

Outcome when cancer has or hasn’t been completely removed.

Sterenchock, Based on Center for Prostate Disease Database

Urology Times, 2004
Did You Know? Recurrence after prostatectomy

Likelihood of biochemical failure (rising PSA) by pre-operative serum PSA.

The Oncologist, 8, 2003 (Johns Hopkins)
Prostatectomy Vs Brachytherapy Based Regimes

Intermediate Risk Group
PSA Failure-free Survivals Per Modality

Freedom from failure after prostatectomy, external radiation or brachytherapy for patients with pre-treatment PSA between 10–20 ng/ml, as reported from leading specialty centers with a reputation for excellence in their modality. (Shipley, Blasko, Pound, Zelefsky, Catalan) The most striking findings are the lack of a plateau in prostatectomy patients with a PSA above 10. This finding, by renowned surgeons, is the reason that more intelligent, discriminating oncologists consider radical prostatectomy to be purely palliative for men with a PSA above 10.
Likelihood of biochemical failure (rising PSA) by pre-operative biopsy Gleason score.
The Oncologist, 8, 2003 (Johns Hopkins)
## How do patients with Gleason Scores ≥ 8 fare with Surgery?

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Institution</th>
<th>Sample Size</th>
<th>Follow-up</th>
<th>Failure Definition</th>
<th>BRFS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>Johns Hopkins University[76]</td>
<td>220</td>
<td>10 yr</td>
<td>PSA &gt; 0.2 ng/mL</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic[77]</td>
<td>584</td>
<td>7 yr</td>
<td>PSA &gt; 0.4 ng/mL</td>
<td>37%-47%</td>
</tr>
<tr>
<td></td>
<td>Memorial Sloan-Kettering[78]</td>
<td>274</td>
<td>10 yr</td>
<td>PSA &gt; 0.4 ng/mL</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td>Northwestern University[79]</td>
<td>237</td>
<td>10 yr</td>
<td>PSA &gt; 0.2 ng/mL</td>
<td>32%</td>
</tr>
</tbody>
</table>

Biochemical Relapse–Free Survival in Prostate Cancer Patients With Gleason Score ≥ 8 Treated With Radical Prostatectomy

Oncology, Vol 22, No 9, 2008
Prostatectomy and Perineural Invasion (PNI)

Should I be concerned?

Biochemical disease-free outcome for a radical prostatectomy (Katz et al\textsuperscript{70}), a three-dimensional conformal radiation therapy (Bonin et al\textsuperscript{75}), and a permanent prostate brachytherapy (Merrick et al\textsuperscript{77}) series stratified by the presence of perineural invasion (PNI)
RECURRANCE AFTER PROSTATECTOMY

Did you know?

PSA Failure-Free Survival following Radical Prostatectomy

D’Amico, Oncology, Vol 15, 2001 (Brigham)
DID YOU KNOW?

PSA Failure-Free Survival in Patients Undergoing Radical Prostatectomy

Stratified by Percent of Positive Prostate Biopsies

D’Amico, Oncology, Vol 15, 2001 (U. Penn)
How to Avoid Recurrence
Problems with radical prostatectomy

Some history:

... on the Influence of Inadequate Operations on the Theory of Cancer:

“Radical Prostatectomy Violates the Principles of Surgical Oncology”

- Charles Moore, MD surgeon, 1867 (U.K.)
Can DaVinci Do Better?
Comparing radical prostatectomy by open retropubic to DaVinci robotic techniques

Journal of Clinical Oncology, Vol 26, No 14, 2008 pp 2278-84 (Harvard Analysis)

“At 6 months, bio-chemical failure increased from 9.1% (open) to 27.8% (DaVinci robotic), with 40% increase in anastomatic strictures (DaVinci robotics)”


“Patients who underwent robotic surgery had significantly higher levels of dissatisfaction and regret than patients undergoing retropubic radical prostatectomy.”


(Question remains as to experience of urologist OR “just another way of cutting out the prostate.” M. Dattoli)
How to Avoid Recurrence
Problems with radical prostatectomy

Some history ...

Dr. William Halstead
Johns Hopkins Hospital, Baltimore, MD:

- “... wide surgical margins are necessary to properly excise cancer (en bloc resection). Cutting through cancerous tissue liberates cancer cells and contaminates the normal systemic circulating blood system ...”
How to Avoid Recurrence
Problems with radical prostatectomy

Some history ...

Prostate resection, envisioned by Dr. Halstead, would amount to total cystoprostatectomy, removal of neurovascular bundles and an ano-rectal resection (aka “pelvic exenteration”) that would leave the patient with a permanent colostomy, urinary diversion and complete erectile dysfunction.
How to Avoid Recurrence
Problems with radical prostatectomy

Some history...

“There are two kinds of people... those who start counting the fingers on their hands, and those who start counting the fingers on their feet. I am a foot-counter.”

- Dr. William Halstead

Johns Hopkins Hospital - Baltimore
What would Dr. Halstead likely say about the DaVinci robot procedure?

“– Just another way of surgically removing the prostate, violating all known cancer principles.”
My cancer has returned after radical prostatectomy.

What do I do?
Salvage Radiation for Local Recurrence

PSA Matters

Salvage Radiotherapy for PSA-Only Recurrence Following Radical Prostatectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Pre-Salvage PSA</th>
<th>Disease-free Outcome at 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al</td>
<td>&gt;2.5</td>
<td>8%</td>
</tr>
<tr>
<td>Forman et al</td>
<td>&gt;2.0 ≤2.0</td>
<td>33% 59%</td>
</tr>
<tr>
<td>Stephenson et al</td>
<td>&gt;2.0 ≤1.0</td>
<td>15% 52%</td>
</tr>
<tr>
<td>Zelefsky et al</td>
<td>&gt;1.0 ≤1.0</td>
<td>17% 74%</td>
</tr>
</tbody>
</table>

Scionti, AUA, 2004
SWOG 8794 – Patterns of failure associated with high-risk Prostate Cancer

Adjuvant radiation matters!

Sentinel Node-based IMRT for Prostate Cancer
Int J. Rad Onc, Vol 67, No 2, 347-355
Salvage Radiation for Local Recurrence

Radiation Following Prostatectomy

Rationale for combining hormone therapy and adjuvant/salvage radiation

- SWOG 8794
- EORTC (Bolla)
- RTOG 94-13
- RTOG 92-02
- RTOG 85-13
- RTOG 86-10
- Messing, NEJM, Vol 341, 1999
Did You Know? Recurrence after prostatectomy

Likelihood of biochemical failure (rising PSA) by pre-operative serum PSA.

The Oncologist, 8, 2003 (Johns Hopkins)
Prostatectomy Vs Radiation

How does External Beam Measure Up?
Did you know?

Long-term 3D-CRT Data

Hanks, IJROBP, Vol 54, 2002 (Fox Chase)

FAV  Gleason 2-6, no peri-neural invasion
UNFAV  Gleason 7-10  peri-neural invasion
Did you know?

3D Conformal Radiotherapy

University of Michigan
RECURRANCE AFTER RADIATION

Did you know?

PSA Failure-Free Survival following 3D-CRT

D’Amico, Oncology, Vol 15, 2001 (Brigham)
Did you know?

IMRT Results Per Prognostic Risk Group

Zelefsky et al, J of Urol., 166, 2001
Does Dose Matter?

MDACC 3D Protocol
Final Analysis: PSA >10

%6 yr FF(n)
78 Gy: 62(53)
70 Gy: 43(53)

Pollack et al, 2003
IMRT: YES! Dose Does Matter.

Zelefsky et al, J of Urol, 166, 2001
A Comparison of Radiotherapy Modalities for Treatment of Localized (loco-regional) Prostate Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Typical Dose</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-CRT</td>
<td>7000-8500cGy</td>
<td>Fractionated</td>
</tr>
<tr>
<td>IMRT (4D IG-IMRT)</td>
<td>7000-9100cGy</td>
<td>Fractionated</td>
</tr>
<tr>
<td>IGRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protons/Neutrons</td>
<td>7000-8500cGy</td>
<td>Fractionated</td>
</tr>
<tr>
<td>CyberKnife</td>
<td></td>
<td>Dose investigational</td>
</tr>
<tr>
<td>Rapid Arc Radiation</td>
<td>7000-9100</td>
<td>Fractionated</td>
</tr>
<tr>
<td>(Radiation Dose Rate Investigational)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pd-103/I-125</td>
<td>12,5000cGy/14,400cGy</td>
<td>Continuous</td>
</tr>
<tr>
<td>Brachytherapy (Monotherapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDR Ir-192 (Monotherapy)</td>
<td></td>
<td>Dose investigational</td>
</tr>
<tr>
<td>All forms of EBRT and HDR Ir-192</td>
<td>4000-5000cGy (EBRT-HDR) 1500-2500cGy (Brachy-HDR)</td>
<td>Fractionated</td>
</tr>
<tr>
<td>3D-CRT/IMRT (4D IG-IMRT) and Pd-103/I-125</td>
<td>4000-5400cGy</td>
<td>Fractionated</td>
</tr>
<tr>
<td></td>
<td>8000-12,000cGy</td>
<td>Continuous</td>
</tr>
</tbody>
</table>
Prostate Brachytherapy: An Historical Perspective

JAMA, 1917

“...because of the initial success of radium treatment, I now take the stand that no patient with prostate cancer should be operated on...”

Barringer, Chief of Urology
Memorial Sloan-Kettering Cancer Ctr.
New York City
The Case for Brachytherapy Alone or Combination Radiation/Brachytherapy
Prospective Randomized Multi-Center Trial

Purpose: To evaluate Urethral/Rectal Morbidity (Intermediate follow-up, 1-12 months)

I-125 Monotherapy (n=44)
Low Risk: (144 Gy, TG-43)
Pd-103 Monotherapy (n=51)
(125 Gy, NIST-99)

44 Gy 3D-CRT → 90 Gy Pd-103 (n=51)

Intermediate to high risk:
20 Gy 3D-CRT → 115 Gy Pd-103 (n=57)

Prostate Brachytherapy and Supplemental Beam Radiation (cont.)

Results:

- AUA Score at 1 month highest in patients treated with Pd-103 to highest prescription dose (Pd-103 alone, 125 Gy or 20 Gy → Pd-103, 115 Gy)
- AUA Score at 6 months highest in I-125 Monotherapy group
- Rectal morbidity similar between all treatment groups aside from slight increase Grade II at 1 month in patients treated with Pd-103 or 125 Gy Monotherapy Groups
- No instance of rectal ulceration or fistulas
* At no point did supplemental 3D-CRT affect post-implant AUA scores or rectal morbidity.

How do Brachytherapy Based Regimens Measure Up?
Composite Radiation and Seeding at the Dattoli Cancer Center
Recurrent Prostate Cancer
Who is most at risk?

Current NCCN Staging Guidelines

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<td>Intermediate Risk: Stage $T_{2b} - T_{2c}$, or Gleason 7, or PSA 10-20</td>
<td>$\leq 50%$</td>
</tr>
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<td>High Risk: Stage $\geq T_{3a}$, or Gleason 8-10, or PSA $&gt; 20$</td>
<td>$&gt; 50%$</td>
</tr>
</tbody>
</table>
How do Patients Having Intermediate to High-Risk Disease Fare with Combination Radiation/Brachytherapy?
The “Perfect Treatment”

The PERFECT Treatment for the PERFECT Patient in a PERFECT World
Figure 4: Survival After Brachytherapy vs Prostatectomy, by Gleason Score—Biochemical relapse-free survival among patients with Gleason score 8–10 treated definitively with brachytherapy and supplemental external-beam radiation (red) or radical prostatectomy (black).
Figure 5: Survival After Brachytherapy vs Prostatectomy, by PSA Level—Biochemical relapse-free survival among patients with prostate-specific antigen (PSA) > 20 ng/mL treated definitively with brachytherapy and supplemental external-beam radiation (red) or radical prostatectomy (black).
**HOW TO AVOID RECURRENCE**

How about combined Radiation and Brachytherapy in patients having high grade cancers?

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Criteria</th>
<th>5-Year Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dattoli Cancer Center[15]</td>
<td>52</td>
<td>16 yr</td>
<td>PSA &gt; 0.2 ng/mL; and nadir + 2 ng/mL</td>
<td>80% (Gleason 8-9)</td>
</tr>
<tr>
<td>Seattle Prostate Institute[3]</td>
<td>23</td>
<td>15 yr</td>
<td>2 consecutive PSA rises</td>
<td>61%</td>
</tr>
<tr>
<td>Mount Sinai[11]</td>
<td>124</td>
<td>7 yr</td>
<td>ASTRO consensus</td>
<td>77.5%</td>
</tr>
<tr>
<td>Schiffler Cancer Center[14]</td>
<td>120</td>
<td>10 yr</td>
<td>PSA &gt; 0.4 ng/mL</td>
<td>89% (+ADT)</td>
</tr>
<tr>
<td>Puget Sound VA Hospital[80]</td>
<td>47</td>
<td>5 yr</td>
<td>PSA &gt; 0.5 ng/mL</td>
<td>56% (Gleason 8)</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering[81]</td>
<td>57</td>
<td>7 yr</td>
<td>Modified ASTRO consensus</td>
<td>51% (Gleason 8)</td>
</tr>
<tr>
<td>Radiotherapy Clinics of GA and Georgia Urology[71]</td>
<td>49</td>
<td>10 yr</td>
<td>PSA &gt; 0.2 ng/mL</td>
<td>60%</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; ASTRO = American Society for Therapeutic Radiology and Oncology; BRFS = biochemical relapse–free survival; EBRT = external-beam radiation therapy; PSA = prostate-specific antigen.
... but I’ve already been treated and my cancer has returned! What do I do now?

### Potential Strategies

<table>
<thead>
<tr>
<th>Initial Treatment</th>
<th>Salvage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatectomy</td>
<td>EBRT (preferably more advanced than IMRT) ADT</td>
</tr>
<tr>
<td>EBRT</td>
<td>Prostate Brachytherapy ADT, Cryosurgery, HIFU, Biothermy, Prostatectomy</td>
</tr>
<tr>
<td>Prostate Brachytherapy</td>
<td>Salvage Brachytherapy IMRT DART ADT, Cryosurgery, HIFU, Biothermy, Prostatectomy</td>
</tr>
<tr>
<td>Other</td>
<td>Watchful waiting/expectant surveillance</td>
</tr>
</tbody>
</table>
Is Locally Advanced High Risk Prostate Cancer Incurable?
Is High-Risk Prostate Cancer Incurable?
Supplemental Radiation and Prostate Brachytherapy

For Patients having High-Risk Malignancies

![Graph showing biochemical survival rates for different treatment strategies.]

Figure 5: Postbrachytherapy Survival in High-Risk Patients—Biochemical outcome for hormone-naive high-risk patients. XRT = external-beam radiation therapy.[2,4,7,41]

From Oncology, Vol 20, No 5, 2006
Long-term outcomes for patients with prostate cancer having intermediate and high-risk disease, treated with brachytherapy and supplemental conformal radiation.

Michael Dattoli, MD; Kent Wallner, MD; Lawrence True, MD
David Bostwick, MD; Jennifer Cash, ARNP; Richard Sorace, MD, PhD
Dattoli Cancer Center & Brachytherapy Research Institute
Sarasota, Fl
University of Washington
Seattle, WA
Journal of Oncology, July 2010
Supplemental Radiation and Pd-103 Brachytherapy for patients having Intermediate to High-risk Cancer
16 Year data

Materials and Methods 1/92 - 2/97

321 Consecutive Patients treated by one author (MD)

Selection Criteria

Patients stratified per NCCN guidelines

157 patients had intermediate risk disease

\[ T_{2B} / T_{2C} \] or Gleason 7 or PSA 10.1-20

164 patients had high risk disease

\[ \geq T_{3A} \] or Gleason 8-10 or PSA >20

Other: 79 patients had elevated PAP

Dattoli et al, Journal of Oncology, July 2010
Materials and Methods

Patients were followed at 3, 6 and 12 months and every 6-12 months thereafter

* Definition of Biochemical Success: PSA <0.2, nadir +2 and ASTRO Consensus Definition

Follow-up saturation biopsy were performed on all failing patients

* Biochemical data independently re-reviewed and analyzed by Kent Wallner, MD (University of Washington)

* Original biopsy slides re-reviewed by Lawrence True, MD (University of Washington)

Dattoli et al, Journal of Oncology, July 2010
16 Year data

Patient characteristics

Mean PSA 19.4 (1.6 – 147)
Median PSA 16.4
218 patients had Gleason Score 7-10
   (52 patients Gleason 8-10)
203 patients had PSA >10 with 78 patients having PSA >20
141 patients had clinical stage T$_{2C}$
127 patients had clinical stage $\geq$T$_{3A}$
79 patients had elevated PAP’s and were analyzed separately

Other:

Follow-up – 16 year actuarial (median 10.5 years)

Dattoli et al, Journal of Oncology, July 2010
RESULTS

82% overall actuarial freedom from biochemical relapse at 16 years using strict PSA criteria (89% intermediate; 74% high-risk)

(Freedom from failure calculated by method of Kaplan-Meier. Difference between groups determined by log rank or student’s t-test) 86% cancer specific survival.

Absolute risk of failure fell to 1% beyond 6 years after treatment.

Dattoli et al, Journal of Oncology, July 2010
16 Year data

Conclusions

These results coupled with numerous other series suggest that brachytherapy based regimens should be considered the standard of care in properly selected patients having intermediate to high-risk disease.

Dattoli et al, Journal of Oncology, July 2010
Detecting Prostate Cancer Recurrence using Advanced Technologies
Local Diagnostics
Staging Studies

- CFD TRUS
- TRUS Elastography
- DCE-MRI
- MRSI
Regional/Distant diagnostic Staging studies

- Combidex/Sinerem MRI
- $^{18}$F-FDG fluoride PET/CT
- $^{11}$C – Choline PET/CT (awaits FDA approval)
- await Combidex alternatives
Noninvasive Detection of Clinically Occult Lymph-Node Metastases in Prostate Cancer

Mukesh G. Harisinghani, M.D., Jelle Barentsz, M.D., Ph.D., Peter F. Hahn, M.D., Ph.D., Willem M. Deserno, M.D., Shahin Tabatabaei, M.D., Christine Hulsbergen van de Kaa, M.D., Ph.D., Jean de la Rosette, M.D., Ph.D., and Ralph Weissleder, M.D., Ph.D.
33 of 33 patients having prostate lymph node metastasis were successfully identified following lymph node dissection/sampling.

NEJM 2003: 248, 2491-2498
Further analysis:

- Positive Predictive Accuracy = 95%
- Negative Predictive Accuracy = 96%

Conclusion:
High predictive accuracy! May proceed to local-regional therapy without performing PLN dissection.

Lancet Oncology, 2008
The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: $^{99m}$Tc-MDP Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT

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The aim of this study was to compare the detection of bone metastases by $^{99m}$Tc-methylene diphosphonate ($^{99m}$Tc-MDP) planar bone scintigraphy (BS), SPECT, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT in patients with high-risk prostate cancer. **Methods:** In a prospective study, BS and $^{18}$F-Fluoride PET/CT were performed on the same day in 44 patients with high-risk prostate cancer. In 20 of the latter patients planar BS was followed by single field-of-view (FOV) SPECT and in 24 patients by multi-FOV SPECT of the axial skeleton. Lesions were interpreted separately on each of the 4 modalities as normal, benign, equivocal, or malignant. **Results:** In patient-based analysis, 23 patients had skeletal metastatic spread (52%) and 21 did not. Categorizing equivocal and malignant interpretation as sugges-

**Conclusion:** $^{18}$F-Fluoride PET/CT is a highly sensitive and specific modality for detection of bone metastases in patients with high-risk prostate cancer. It is more specific than $^{18}$F-Fluoride PET alone and more sensitive and specific than planar and SPECT BS. Detection of bone metastases is improved by SPECT compared with planar BS and by $^{18}$F-Fluoride PET compared with SPECT. This added value of $^{18}$F-Fluoride PET/CT may beneficially impact the clinical management of patients with high-risk prostate cancer.

**Key Words:** PET-CT; $^{18}$F-Fluoride; SPECT; bone metastases; prostate cancer

Biopsy proven solitary skeletal metastatic prostate cancer.
$^{18}$F-FDG Fluoride PET/CT
note: right pelvic lymphadenopathy.
NOTE: Left neurovascular bundle involvement
location, location, location!

FIGURE 4. MRI of prostate with 3TP software overlay showing contrast kinetics with matching whole mount specimen from a radical prostatectomy. There is excellent correlation between the red areas indicating areas of high contrast inflow and washout consistent with cancer in the peripheral zone and the whole mount specimen, where the cancer is circled in red. (Provided by 3TP)

DCE- MRI Show me the capsule!
DCE-MRI S/P radical prostatectomy on patient having rising PSA

At the location of the old tumor, there is strong enhancement on the DCE-MRI. A biopsy confirmed prostate cancer recurrence.
Prostate Analysis using Color Flow Doppler for Staging
NOTE: This tumor involves the entire posterior peripheral zone
CFD demonstrating a malignant lesion

Patient S/P EBRT
Color Flow Doppler for Tumor Delineation/Targeting

NOTE: Dominant lesion, left posterior – lateral peripheral zone
Elastography images of a prostate with a Gleason Score 6 in the left peripheral zone (biopsy-proven carcinoma). Elastography visualizes relative tissue stiffness—dark blue indicates more stiffness in comparison to surrounding tissue shown in green and red.
3D Color-Flow Doppler Utilized as Follow-up S/P Brachytherapy

NOTE: Color-Flow Doppler demonstrating absence of cancer S/P Brachytherapy
Follow-up TRUS with CFD s/p Brachytherapy

Biopsy proven recurrent malignancy, right mid-gland visualized only with CFD

PSA 0.1
Follow-up TRUS with CFD s/p Prostatectomy

Biopsy proven malignancy within lower prostatic bed.
What’s New?

D A R T
Combined Modality Treatment for Prostate Cancer With Dynamic Adaptive Radiation Therapy Using Four-Dimensional Image-Guided Intensity-Modulated Radiation Therapy and Brachytherapy

Jennifer C. Cash, ARNP, MS, OCN; Jone Fay, BS, (R)(T), CMD; and Michael J. Dattoli, MD

ABSTRACT: Prostate cancer can be successfully treated using dynamic adaptive external beam radiation techniques along with interstitial brachytherapy to deliver curative therapies with low urinary, rectal and erectile function morbidity. Through the use of sophisticated, state-of-the-art radiographic imaging for staging and treatment planning, a precise, individual design for treatment is accomplished. Symptom management and patient education are of paramount importance and are integrated throughout the treatment process. (J Radiol Nurs 2009:28:87-95.)

KEYWORDS: IMRT; DART; Brachytherapy; Prostate cancer.
Behold:

the 4\textsuperscript{th} Dimension

MOTION
D A R T Dose Painting

Bladder
Rectum
PTV2
CC
Bulb

P.P.T.
What’s New?

It’s all about Motion!

D A R T

and

Analysis Tools
What’s New?

Analysis Tools for Image Guidance for DART

- Echo Guidance Systems

1st Generation

- **BAT** (Ultrasound based **B**-mode **A**cquisition and **T**argeting); 2 dimensional

3rd Generation

- **SonArray® 3D** Virtual Ultrasound Acquisition, with Remote Capabilities, Optical Camera Based Tracking Subsystem for immediate system default; allows for intra-fractional motion gating for Dynamic **Adaptive** Radiotherapy (DART)
What’s New?

Analysis Tools for Image Guidance

- Other

• Respiratory Gating – advanced video tracking technology which allows for real-time monitoring and correction of physiologic motion of prostate which may occur as a result of patient breathing (also for Adaptive Radiotherapy)
D A R T and Respiratory Gating

Increase Treatment Time by × 2.5 (25% Duty Cycle)

Inspiration: 2.0 Sec.
Expiration: 3.5 Sec.

Normal Respiration
Cough
Beam-On
Beam-off

INHALE
EXHALE

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Analysis Tools for Image Guidance

- **Other**

- Exact Table
- Electronic On-line Portal Imaging ("Portal Vision") using amorphous silicon diode technology which allows for real-time on-line verification of patient’s exact treatment plan
- 3rd Generation Cone Beam Tomography - real-time helical CT anatomical reconstruction of patient’s anatomy to determine the actual daily delivered dose (also for “Adaptive Radiotherapy”)
Cone Beam CT for D A R T
What’s New?

4D Adaptive IG-IMRT and “Biologically Directed Radiation”

• Biologic Variables to selectively target areas of higher tumor burden – identify tumor metabolism
  – Color Flow Doppler Ultrasound
  – MRI Spectroscopy
  – Dynamic Contrast Enhanced MRI (DCE-MRI)
  – ProstaScint® Fused with Helical CT, MRI, etc
  – High Resolution MRI following administration of lymphotrophic super-paramagnetic ferrous oxide nano-articles (USPIO, Combidex, Ferumoxtran-10)
  – PET using F-18 Fluorocholine

FUSION (combining the above)
D A R T

and

Dose De-Modulation/Escalation Using Fusion Techniques

at Dattoli Cancer Center & Brachytherapy Research Institute Sarasota, Florida

Michael J. Dattoli, MD
Color Flow Doppler Ultrasound and Fusion Techniques for D A R T Dose Intensification
Color-flow Doppler for D A R T /Brachytherapy Fusion and Dose Optimization

NOTE: CFD, left base peripheral lesion, axial image
My Combidex is positive! What do I do?
Fused CT/MRI Combidex
Plus DCE-MRI and CFD
for
D A R T
Treating abdominal or para-aortic nodes.
Combidex nodes in the pelvis are treated using the same angles as are used with pelvic DART.
D A R T: Tumor Dose Escalation / Urethral Dose Demodulation
D A R T and Precise
Tumor Dose Delineation
What’s New?

D A R T: An alternative to Proton Beam Therapy?

• Inverse treatment planning capabilities with constraints allow for superior beam (“beamlet”) arrangements and therefore superior dosimetry to target(-s) not possible with protons
• Image guided methods for Interfractional verification
  – SonArray® (3rd Generation)
  – Electronic on-line portal imaging (“Portal Vision”)
  – On-board Imaging
  – Exact “couch” (table)
  – Cone Beam Tomography
What’s New?

D A R T:
An alternative to Proton Beam Therapy?

- Image Guided methods for Intrafractional motion gating
- Cone Beam CT – Real-time 3D verification (reconstruction of the actual daily delivered dose based on the patient’s anatomy in real-time)
  - SonArray® 3D Ultrasound with camera-based localization for intra-fractional motion gating
  - Respiratory gating – corrects for target movement 2° breathing patterns
What’s New?

D A R T:
An alternative to Proton Beam Therapy?

BOTTOM LINE: Margin of Error $\leq 0.5$ mm
Far higher doses can be safely delivered!

An alternative to Proton Beam Therapy?

ABSOLUTELY!
• The Right Dose
• The Right Place
• The Right Time

Biologic and D A R T

4D IG-IMRT
And Dynamic Targeting

CTV=PTV

Prostate
Rectum
Conclusion:

DART plus Palladium-103 allows for dose escalation within the prostate while keeping penile bulb and corporal body doses significantly reduced, when compared to IMRT or IGRT.
The Evolution is now the Revolution using DART ± Pd-103.
“NEW” does not mean “BETTER” - See “The Facts”
# Prostate Cancer Treatment Options

<table>
<thead>
<tr>
<th>Treatment Name(s)</th>
<th>Description</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy/</td>
<td>As primary treatment, uses the process of freezing and thawing to destroy cancer cells.</td>
<td>No cutting, performed on outpatient basis.</td>
<td>Highest risk of incontinence and can typically occur. Despite good pain management during treatment, long-term effects may be minimal. Generally recommended for patients with high-risk features.</td>
</tr>
<tr>
<td>Cytostatication</td>
<td>Eg. Cryo-surgery, typically used in conjunction with cryosurgery.</td>
<td>Can be repeated.</td>
<td></td>
</tr>
<tr>
<td>Cyberknife</td>
<td>Fancy name, actually a method of radiation: “hyper-fractured” dose delivery (deeper to 24 Gy, closer to 18 Gy). Higher doses of radiation.</td>
<td>Treatment usually delivered in only a few fractions.</td>
<td>All extreme radiation hypoxia/dense scarring can include high incidence of skeletal bone problems.</td>
</tr>
<tr>
<td>High Intensity</td>
<td>Uses focused sound waves from a rectal probe to ablate cancer cells. Waves heat the target area to destroy tissue. Several hours to days.</td>
<td>Non-invasive (treatment can be repeated).</td>
<td>Just another form of “hypothetical” – heat abandoned as cancers virtually always return.</td>
</tr>
<tr>
<td>Hormonal Therapy</td>
<td>Uses various types of hormones to decrease production of testosterone to inhibit growth and progression of cancer.</td>
<td>Easy one and/or injection treatment.</td>
<td>Side effects: complete erectile dysfunction (not reversable), weight gain, fatigue, tenderness.</td>
</tr>
<tr>
<td>Radiation:</td>
<td>Different types of radiation and different delivery systems to kill cancer cells.</td>
<td>No cutting, no blood loss; no risk of infection.</td>
<td>Potential of over-radiation eliminated by external boosters.</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Implanting radioactive sources (seeds, cells) directly into the tumor.</td>
<td>Ability to place radiation source exactly at tumor site.</td>
<td>Results depend on quality of brachytherapists who deliver and maintain.</td>
</tr>
<tr>
<td>Palladium-123</td>
<td>Longer half-life and wider dose area.</td>
<td>Better effects than I-131 or Cs-131.</td>
<td>If not performed by highly experienced physicians, can increase side effects.</td>
</tr>
<tr>
<td>Iodine-125</td>
<td>Longer half-life and wider dose area.</td>
<td>Less penetrating than I-131 or Cs-131.</td>
<td>Serves as effective palliative treatment, especially in advanced cases.</td>
</tr>
<tr>
<td>High Dose Rate</td>
<td>Using high-intensity focused ultrasound.</td>
<td>Use of new microprocessors.</td>
<td></td>
</tr>
<tr>
<td>COMBINATION</td>
<td>Using two or more types of radiation, sometimes with hormones, to defeat cancer.</td>
<td>Cancers of all sites proven to respond best to multiple modalities of treatments.</td>
<td></td>
</tr>
<tr>
<td>EBRT</td>
<td>External Beam Radiation uses “fractured” photon doses.</td>
<td>Early version of technology.</td>
<td>Outdated technology with many side effects.</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy with protons.</td>
<td>More controlled versions.</td>
<td>New “old” technology.</td>
</tr>
<tr>
<td>Neutron Therapy</td>
<td>Using neutrons to kill cancer cells.</td>
<td>Theoretically might be effective for treating cancer resistant to photon radiation.</td>
<td>Any contact with healthy tissue can cause severe side effects. Various “doses” and various cell types.</td>
</tr>
<tr>
<td>Proton Therapy</td>
<td>Uses Proton beams to kill cancer cells.</td>
<td>Excellent treatment for very small tumors in the prostate gland.</td>
<td>Risks of radiation “scarring,” not effective for secondary tumors from prostate by-product.</td>
</tr>
<tr>
<td>RapidArc9</td>
<td>New product from Vision, using a single radiation technique.</td>
<td>Shorter treatment times (patient reduced to 3-5 hours and less)</td>
<td>Problems with consistent movement of sources. Under-treatment and excessive treatment times can cause serious problems.</td>
</tr>
<tr>
<td>Tomotherapy</td>
<td>Computed tomography guided IMRT</td>
<td>In theory, delivers radiation in matched pattern to best used for small targets.</td>
<td>Misconception of guarantee that all cancers are cured.</td>
</tr>
<tr>
<td>Surgery:</td>
<td>“The old ‘gold’ standard.”</td>
<td>Performed as best method to eradicate any cancer.</td>
<td>Most aggressive surgery to be performed on very aggressive cancers. May cause severe complications.</td>
</tr>
<tr>
<td>Radical</td>
<td>Surgery removes the bulk of the gland by either en bloc or perineal.</td>
<td>Surgically removes the bulk of the gland by en bloc or perineal.</td>
<td>Most aggressive surgery performed on advanced cancers. May cause severe complications.</td>
</tr>
<tr>
<td>Robotic “da Vinci”</td>
<td>Uses “laparoscopic” robotic equipment to remove gland tissue through small incisions in the abdomen.</td>
<td>“Robotic assistance” reduces chance of complications.</td>
<td>Most aggressive surgery to be performed on advanced cancers. May cause severe complications.</td>
</tr>
<tr>
<td>Watchful</td>
<td>No treatment but periodic testing to assess disease progression.</td>
<td>No treatment is easiest to tolerate as long as cancer does not spread.</td>
<td>Difficult for patient—“watchful waiting” in the aggressive and PPSs may even be difficult.</td>
</tr>
</tbody>
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| Full chart available from Dattoli Cancer Foundation Booth - | 123 |