Pathology of Aggressive Prostate Cancer
Intraductal Carcinoma and Cribriform Carcinoma

Dr. Michelle Downes, Staff Urologic Pathologist
Sunnybrook Health Sciences Centre, Toronto
Assistant professor, LMP, University of Toronto
Overview

• Prostate Cancer

• What is *intraductal carcinoma*?

• The case for *cribriform* pattern invasive carcinoma

• Clinical evidence for its prognostic impact

• Molecular underpinnings
Prostate Cancer

Main change is the Gleason grade 3 and 4 groups

SEER Data US

ISUP Grade Groups

TABLE 1.2 Projected new cases and age-standardized incidence rates (ASIR) for cancers, by sex, Canada, 2017

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Total* (2017 estimates)</th>
<th>New cases</th>
<th>Cases per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>All cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>28,600</td>
<td>14,400</td>
<td>14,200</td>
</tr>
<tr>
<td>Colorectal</td>
<td>26,800</td>
<td>14,900</td>
<td>11,900</td>
</tr>
<tr>
<td>Brain</td>
<td>20,400</td>
<td>9,900</td>
<td>10,500</td>
</tr>
<tr>
<td>Prostate</td>
<td>21,300</td>
<td>21,300</td>
<td>—</td>
</tr>
<tr>
<td>Bladder</td>
<td>8,100</td>
<td>6,700</td>
<td>1,400</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>8,300</td>
<td>4,600</td>
<td>3,700</td>
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<tr>
<td>Uterus (body, NOS)</td>
<td>3,500</td>
<td>1,300</td>
<td>2,200</td>
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<tr>
<td>Melanoma</td>
<td>3,200</td>
<td>2,000</td>
<td>1,200</td>
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<tr>
<td>Thyroid</td>
<td>7,100</td>
<td>1,650</td>
<td>5,450</td>
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<tr>
<td>Kidney and renal pelvis</td>
<td>6,600</td>
<td>4,200</td>
<td>2,400</td>
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<tr>
<td>Leukemia</td>
<td>6,200</td>
<td>3,600</td>
<td>2,600</td>
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<tr>
<td>Pancreas</td>
<td>5,500</td>
<td>2,800</td>
<td>2,700</td>
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<tr>
<td>Oral</td>
<td>4,700</td>
<td>3,200</td>
<td>1,500</td>
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<tr>
<td>Stomach</td>
<td>3,500</td>
<td>2,200</td>
<td>1,300</td>
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<tr>
<td>Brain/CNS</td>
<td>2,000</td>
<td>1,700</td>
<td>1,300</td>
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<tr>
<td>Multiple myeloma</td>
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<td>1,700</td>
<td>1,200</td>
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<tr>
<td>Ovary</td>
<td>1,800</td>
<td>1,200</td>
<td>600</td>
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<tr>
<td>Liver</td>
<td>2,500</td>
<td>1,500</td>
<td>500</td>
</tr>
<tr>
<td>Esophagus</td>
<td>2,300</td>
<td>1,800</td>
<td>500</td>
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<tr>
<td>Colon</td>
<td>1,550</td>
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<td>1,550</td>
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<tr>
<td>Larynx</td>
<td>915</td>
<td>970</td>
<td>40</td>
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<td>Testis</td>
<td>1,100</td>
<td>1,100</td>
<td>—</td>
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<td>Hodgkin lymphoma</td>
<td>990</td>
<td>570</td>
<td>420</td>
</tr>
<tr>
<td>All other cancers</td>
<td>19,500</td>
<td>9,600</td>
<td>9,900</td>
</tr>
</tbody>
</table>

GS 6
GS 7 (3+4)
GS 7 (4+3)
GS 8
GS 9-10

AJSP 2016; 2:244-252
Gleason 4 patterns
What is intraductal carcinoma?

Distension of antecedent prostate ducts and glands by neoplastic cells / lumen spanning
Intraductal carcinoma is NOT

High grade PIN
No distension, not lumen spanning

Ductal adenocarcinoma (aka endometrioid carcinoma)
Variant of invasive carcinoma
Intraductal Carcinoma - Prostatectomy

Intraductal Carcinoma

• ~ 20% of radical prostatectomies
• Associated with
  – ↑ Tumour volume
  – ↑ Stage
  – ↑ Gleason score
  – + Surgical margins
• Independent prognostic factor


Intraductal Carcinoma – A Rediscovery in Biopsies

Prognostic role of intraductal carcinoma in biopsies

- Associated with **advanced stage** in prostatectomy specimens (1)
- Independent predictor of **early biochemical recurrence** and **metastatic disease** after radiotherapy (2)
- Only independent prognosticator for **death of disease** in patients presenting with metastatic prostate cancer (3)

**References:**


**Intraductal carcinoma either isolated or with Gleason score 6 prostate cancer in biopsy is associated with advanced stage cancer and risk of metastatic disease**
The Case For Cribriform Pattern Carcinoma

**Prognostic role for cribriform pattern invasive carcinoma:**
- Presence of cribriform carcinoma in a GS 7 (3 + 4) biopsy is associated with non-organ confined prostate cancer (1)
- Intraductal carcinoma has frequently a cribriform architecture
- *Intraductal carcinoma is often associated with cribriform invasive carcinoma* (2)
- Cribriform carcinoma in prostatectomy is an independent predictor of biochemical recurrence (2), metastatic disease and death (3)

**References:**
Large Cribriform

Intraductal Carcinoma
Nested Case-Control GS 7 Prostatectomy Series – Metastatic Disease / Survival as Outcome Parameter

Study design: 52 cases (with metastasis, disease-specific mortality or both) and 109 controls, matched for age, PSA level and pT stage.

Overall prevalence of G4 sub-patterns:
- Fused: 75%
- Ill-defined: 64%
- Cribriform 48%
- Glomeruloid 25%

Cases: 81% cribriform
Controls: 38% cribriform
Molecular-Genetic Features of IDC

**PGA** higher in **IDC+** than in **IDC-** prostate cancers

**IDC** is feature of BRCA2 carrier-associated prostate cancers

**Increased genomic instability**

Chua et al. A prostate cancer “Nimbosus”: Genomic instability and SchLAP1 dysregulation underpin aggression of intraductal and cribriform subpathologies. Eur Urol, online

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**Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories**

Renée A. Taylor¹, Michael Fraser², Julie Livingston³, Shadrielle Melijah G. Espiritu¹, Heather Thorne⁴,⁵, Vincent Huang⁶, Winnie Lo⁷, Yu-Jia Shiah⁸, Takaoki N. Yamaguchi⁹, Ania Silwinski²,⁶, Sheri Horsburgh³, Alice Meng⁶, Lawrence E. Heisler¹, Nancy Yu², Fouad Youssi³, Melissa Papagrigirs⁷, Mitchell G. Lawrence⁰, Lee Timms⁰, Declan G. Murphy⁰, Mark Frydenberg⁰, Julia F. Hopkins⁰, Damien Bolton⁰, David Clouston⁰, John D. McPherson⁰, Thendronus van der Kwaast¹, Paul C. Routte³,⁴,⁵,⁶, Gail P. Riddle⁰,⁷,⁸ & Robert G. Bristow²,⁸,¹. Nat. Commun. 8, 13671 doi: 10.1038/ncomms13671 (2017).
Molecular Underpinnings

RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SchLAP1

Conclusions:

• Intraductal / cribriform invasive carcinoma can be combined to provide a novel independent histopathological prognosticator on prostate biopsies.

• Intraductal / cribriform invasive carcinomas are distinct at molecular-genetic level (genetically unstable, SChLAP1) and a feature of BRCA2-associated prostate cancer.

• Intraductal / cribriform carcinoma in Gleason 6 and 7 (3+4) cancer can be used as a determinant of clinically significant prostate cancer.

• Routine reporting of intraductal / cribriform invasive carcinoma on biopsies is recommended as it may lead to imaging and therapy intensification.
Thank You!

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