Update on Colorectal Cancer: Integrating the Host Immune Response
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Outline

- A Tale of 2 Patients
- Review current clinical outcomes in colorectal cancer
- Discuss problems with the current pTNM staging system
- Introduce Immunoscore®: Integrating the Host immune response
A Tale of 2 Patients
Chapter One: An Endoscopic Mass, Ascending Colon
A Tale of 2 Patients
Chapter Two: Right Hemicolecctomy
Patient A: Moderately-differentiated adenocarcinoma
pT3N1b
Patient B: Moderately-differentiated adenocarcinoma pT3N1b
Tale of Two Patients

- Both females >60 years old
- Both right-sided tumors
- Both moderately-differentiated adenocarcinoma
- Both invasive into periclorectal soft tissues (pT3)
- Both metastasis to 2 regional lymph nodes (pN1b)
- Neither has distant metastasis
STAGING OF COLON CANCER

STAGE I

STAGE III

STAGE II

STAGE IV

Lymph node

SPREAD OF THE CANCER TO OTHER ORGANS

Stage 0
Chapter Five: Oncologic Management

- Molecular Work-up: Not MSI
- Molecular Work-up: KRAS non-mutated (wild type) = response to EGFR blockade
- Adjuvant 5-FU Chemotherapy
Tale of Two Patients: The Final Chapter

- Patient A: Alive and well at 5 years
- Patient B: Died from disease at 2 years
Colorectal Cancer: Current Outcomes

- Colorectal cancer remains one of the leading causes of cancer-related death worldwide.
- Variable response rates to chemotherapy.
- Up to 25% of Stage I/II patients [no lymph node metastasis] relapse with rapid tumor progression and patient death.
Colorectal Carcinogenesis: Genetic Model

Cancer Staging

- Current oncologic management is based on pTNM
- Introduction of non-anatomic factors: i.e. Gleason score
- Introduction of prognostic factors: i.e. MSI, ER/PR/HER2
- Evolution of “Individualized Therapy”: the “right therapy for the right tumor in the right patient at the right time”
Understanding Cancer: Questions

- Should we view cancer as different molecular diseases affecting the same organ?
- Biological uniqueness of the patient: does the Host immune response play a role in outcome?
- Biomolecular uniqueness of the tumor: are there other biologic parameters that we can measure?
Current Cancer Outcomes: Problems and Perspectives

- Biologically Heterogeneous Patients
- Molecularly Heterogeneous Tumors
- Clinically Heterogeneous Outcomes
Is the pTNM staging system incomplete?
The Missing Piece? Host Immune Response

- The Inflammatory Microenvironment
- The lamina propria is not an innocent bystander
- Intra- and peri-tumoral lymphocytes: the “in-situ immune infiltrate”
In-situ Immune Infiltrate: Studies

- Intratumoral infiltrate confers a survival advantage (*JAMA* 1931)
- Lymphocytes at the invasive margin correlates with better survival (*J Clin Pathol* 1986)
- Ongoing profiling on immune cells in solid tumors including colon, ovary, head and neck, bladder, breast, liver, prostate, melanoma, lung
- “Implications of the tumor immune microenvironment for staging and therapeutics”, *Mod Pathol* 2017 Dec 1
Quantifying the In-situ Immune Infiltrate

Paris, France
Portland, OR, USA
Bern, Switzerland
Houston, TX, USA
Graz, Austria
Rochester, MN, USA
Erlangen, Germany
Toronto, ON, Canada
Madrid, Spain
Melbourne, Australia
Naples, Italy
Sapporo, Japan
Siena, Italy
Tokyo, Japan
Milan, Italy
Xi'an, China
Umea, Sweden
Doha, Qatar
Stockholm, Sweden
Dorchester, UK
Nijmegen, Netherlands

Immuno Score
“Immunoscore®”

- Scoring system based on 2 lymphocyte populations: CD3 and CD8 T cells
- Quantifies these 2 populations at 2 sites within the tumor: core and invasive margin
- Scored using digital pathology
- Scores range from low “I0” to high “I4”
# Quantifying the In-situ Immune Infiltrate

<table>
<thead>
<tr>
<th>Immune contexture</th>
<th>CD3, CD8, CD45RO</th>
<th>Immunoscore</th>
</tr>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td>Cells/mm²</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Centre, Margin</td>
<td></td>
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<tr>
<td><strong>Orientation</strong></td>
<td>Th1, cytotoxic, chemokines, adhesion</td>
<td></td>
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Galon J et al. *J Pathol* 2014
A

B

TMA spot: CT region
CD3 staining

(cutoff value CD3CT: 256 cells/mm²)

C

Immune infiltration

<table>
<thead>
<tr>
<th></th>
<th>CD3</th>
<th>CD8</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>CT:</td>
<td>Hi</td>
<td>Lo</td>
<td>Hi or Lo + Hi or Lo = 0, 1, or 2</td>
</tr>
<tr>
<td>IM:</td>
<td>Hi</td>
<td>Lo</td>
<td>Hi or Lo + Hi or Lo = 0, 1, or 2</td>
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Immunoscore (I) = 0, 1, 2, 3, or 4

An Integrated Staging System: “pTNM-I”
Incorporating the Host Immune Response

- The TNM staging system is incomplete
- The Host immune response is a clinically relevant variable
- An integrated staging system which incorporates both tumor and patient-specific variables is necessary to improve cancer outcomes
- Immunoscore is a compelling idea and has changed our understanding of cancer
Cleveland Clinic

Every life deserves world class care.