Current Status Of Hypoxia And Radiotherapy

PMH 50th 2008

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Oxygen Measurement using Eppendorf Oxygen electrode

Fig. 5. pO₂ frequency distributions of two ductal breast cancers (stage T₂, grade G2) substantiating marked tumor-to-tumor variability in the oxygenation status. n, number of pO₂ measurements.
## Hypoxia and Clinical Outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>Tumor Site</th>
<th>Patients</th>
<th>OS/DFS</th>
<th>Local Cont</th>
<th>Distant Metastases</th>
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<tbody>
<tr>
<td>Fyles, 2002</td>
<td>Cervix</td>
<td>106</td>
<td>Yes</td>
<td>±</td>
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<td>Hockel, 1996</td>
<td>Cervix</td>
<td>89</td>
<td>Yes</td>
<td>±</td>
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<td>Knocke, 1999</td>
<td>Cervix</td>
<td>51</td>
<td>Yes</td>
<td>±</td>
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<tr>
<td>Lyng, 2000</td>
<td>Cervix</td>
<td>40</td>
<td>Yes</td>
<td>±*</td>
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<tr>
<td>Brizel, 1999</td>
<td>H&amp;N</td>
<td>63</td>
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<td>Nordsmark, 1996</td>
<td>H&amp;N</td>
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<td>Nordsmark, 2000</td>
<td>H&amp;N</td>
<td>31</td>
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<tr>
<td>Rudat, 2000</td>
<td>H&amp;N</td>
<td>41</td>
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<td>Stadler, 1999</td>
<td>H&amp;N</td>
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<td>Brizel, 1996</td>
<td>Sarcoma</td>
<td>22</td>
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<tr>
<td>Nordsmark, 2001</td>
<td>Sarcoma</td>
<td>28</td>
<td>Yes</td>
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</table>
MARGINAL PROBABILITY OF DISTANT RELAPSE

\[ P \text{ value} = 0.0028 \]
Clinical Implications of Tumour Hypoxia

Pitson et al. (IJROBP 2001)
Hypoxia in Clinical Practice

Oxygen measurements to select patient for PA RT
Hypoxia in Clinical Practice

Oxygen measurements to select patient for PA RT
Hypoxia Is Not Related to Anemia

Hypoxia vs. Hemoglobin In Cervix Cancer

Heterogeneous CA9 staining of STS
Summary

• Hypoxia is heterogeneous in tumours and is associated with poor treatment outcome
• Hypoxia is associated with metastatic disease (including nodal disease)
• Hypoxia is associated with poor local control in head and neck cancer but not cervix cancer
• Anemia is not related to hypoxia
Tumor Interstitial Fluid Pressure

- ↑ Capillary permeability
- Abnormal lymphatics
- ↑ Cytokines (PDGF)

↑ Interstitial fluid
Distension of interstitial matrix
↑ IFP

Fibroblast activation
Contraction of interstitial collagen

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Long-Term Performance of IFP and Hypoxia in Cervix Cancer – RT Alone

5 year DFS was 58% in patients with oxygenated tumours and 42% for patients with hypoxic tumours (p=0.05)

5 year DFS was 63% in patients with low IFP and 42% for patients with high IFP (p=0.001)
### Hypoxia vs. IFP – Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>HP$_5$</th>
<th>IFP</th>
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<tbody>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN’s</td>
<td></td>
<td>Yes</td>
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<tr>
<td>Pelvic recurrence</td>
<td>Yes</td>
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<tr>
<td>Distant recurrence</td>
<td>Yes</td>
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</table>
Hypoxia and IFP in Cervix Cancer: Treatment with RT-CT

Hypoxia marginally significant, IFP not significant
Hypoxia in Cervix Cancer

**RT vs Chemo-RT**

**HYPOXIC group, HP5>50**

RT+Cis vs. RT, HR=0.61, 95% CI: 0.38-0.99, Log-rank p-value=0.045

- RT, n=52, 3y DFS=42%
- RT+Cis, n=98, 3y DFS=57%

**OXIC group, HP5<=50**

RT+Cis vs. RT, HR=0.98, 95% CI: 0.55-1.74, Log-rank p-value=0.93

- RT, n=54, 3y DFS=66%
- RT+Cis, n=66, 3y DFS=63%
IFP in Cervix Cancer

RT vs Chemo-RT

HIGH IFP group, IFP > 17.5
RT+Cis vs. RT, HR=0.62, 95% CI:0.37-1.02, Log-rank p-value=0.056
- RT, n=57, 3y DFS=44%
- RT+Cis, n=73, 3y DFS=57%

LOW IFP group, IFP <= 17.5
RT+Cis vs. RT, HR=1.5, 95% CI:0.82-2.76, Log-rank p-value=0.19
- RT, n=45, 3y DFS=71%
- RT+Cis, n=85, 3y DFS=57%

Time to relapse or death (years)

Disease-free Survival
Hypoxia and High IFP Predict for Chemo-RT Response in Cervix Cancer

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### IFP in Cervix Cancer

#### Multivariate Analysis: DFS

<table>
<thead>
<tr>
<th></th>
<th>Low IFP</th>
<th>HR</th>
<th>p</th>
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<tbody>
<tr>
<td>Size</td>
<td>1.38</td>
<td>0.0002</td>
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<tr>
<td>Equivocal LN’s</td>
<td>2.22</td>
<td>0.029</td>
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<tr>
<td>Positive LN’s</td>
<td>1.74</td>
<td>0.12</td>
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<tr>
<td>RT vs. RTCT</td>
<td>0.81</td>
<td>0.51</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>High IFP</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>1.27</td>
<td>0.0024</td>
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<tr>
<td>Equivocal LN’s</td>
<td>1.4</td>
<td>0.33</td>
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<tr>
<td>Positive LN’s</td>
<td>2.13</td>
<td>0.035</td>
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<tr>
<td>RT vs. RTCT</td>
<td>2.01</td>
<td>0.025</td>
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</table>
Summary
Hypoxia and IFP Interaction with Cisplatin

• Prognostic effect of IFP and hypoxia was diminished with addition of chemo to RT
• This appears to be due to a differential effect of chemo
• CT marginally improved DFS compared to RT alone in hypoxic tumors, independent of clinical prognostic factors
• CT significantly improved DFS compared to RT alone in high IFP tumors, independent of clinical prognostic factors
Possible Mechanisms: Hypoxia and IFP Interaction with Cisplatin

Hypoxia

- Hypoxia sensitizes cells to cisplatin by ↓ DNA repair
- Hypoxic tumors are more likely to have occult metastatic (nodal) disease and greater opportunity to benefit from cisplatin

IFP

- Inconsistent with drug delivery effect
- Rapidly proliferating tumors have high IFP and are more sensitive to cisplatin
- High IFP influences cisplatin biodistribution or metabolism
Conclusions

- IFP and hypoxia are independent predictors of survival in cervix cancer.
- High IFP is associated with both local and distant recurrence.
- IFP and hypoxia may be biomarkers of chemo-RT response.
- IFP is also a marker of angiogenesis, a promising therapeutic target in cancer.
- IFP may be a useful marker of biologic response to anti-angiogenic treatment.
Hypoxic Biomarkers in Clinical Development

Extrinsic
- Hypoxia Probes
- Pimonidazole, EF5

Intrinsic
- CA IX, HIF, osteopontin

Hypoxia Imaging
- PET
- DCE-MR and CT

Triple overlay HIF, CA IX and EF5

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DFS curves for CA-IX or HP5 (Toronto)

CA-IX and Cervix Ca outcome – DFS, mets and local control (Manchester)

Log rank p-value = 0.75

Log rank p-value = 0.022

Fig. 4. Disease-specific survival (a), metastasis-free survival (b), and local control (c) in relation to the presence or absence of significant CA IX expression in 130 cervical cancer patients treated with radical radiotherapy.
Locoregional Control and Overall Survival According to the Combined Status of HIF-2 and CA9

A 100
 80
 60
 40
 20

Locoregional Control (%)

Follow-Up (years)

HIF-2α (-)/CA-9 (-)
HIF-2α (+)/CA-9 (-)
HIF-2α (-)/CA-9 (+)
HIF-2α (+)/CA-9 (+)

B 100
 80
 60
 40
 20

Survival (%)

Follow-Up (years)

HIF-2α (-)/CA-9 (-)
HIF-2α (+)/CA-9 (-)
HIF-2α (-)/CA-9 (+)
HIF-2α (+)/CA-9 (+)
Cervix Hypoxia Collaboration

Goal
- to develop a panel of hypoxia-associated markers
- to validate hypothesis that chemo-RT is of benefit only in hypoxic tumours

- Databases and tumour banks form Calgary (n=150), Vancouver (n=50) and PMH (n=150)
- TMA’s to be analyzed in Calgary using HistoRx (Tony Magliocco)
Phase I/II Study of Sorafenib in Patients With Cervix Ca

**Phase I: Sorafenib**

- **DL -1**: 100 mg bid, n=3-6
- **DL 1**: 200 mg bid, n=3-6
- **DL 2**: 400 mg bid, n=3-6

**Phase II: Sorafenib 400 mg bid**, n=30

- **External RT + Cisplatin 40 mg/m^2**

Biomarkers at weeks -2, 0, 2
(pO_2, IFP, fCT, dMRI, MVD, VEGF,...)
Response to Sorafenib: DCE MR

Patient 1
Cervix
T2b N0

Baseline
Day 7 of Sorafenib
Day 21, S+RT

Patient 2
Cervix
T1b N1

Baseline
Day 7 of Sorafenib
Day 21, S+RT

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Clinical Implications

• Drugs targeted at IFP/angiogenesis and hypoxia will likely be effective only in selected patients

• Biomarker assays or imaging are necessary to optimize use of such agents

• Best markers still to be established
Biomarker Conclusions

• Multiple hypoxic markers are prognostic in patients with head and neck and cervix cancer
• Osteopontin and FMISO PET are predictive of response to hypoxic sensitizers/cytotoxins
• TPZ has promise and is undergoing evaluation in Phase III RCT
• Biologically-targeted agents are in Phase I/II trials in combination with radiation and chemotherapy
## Hypoxia in Prostate Cancer

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Method</th>
<th>% Hypoxic</th>
<th>Median $pO_2$ (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>PMH</td>
<td>Inter $pO_2$</td>
<td>35%</td>
<td>6.7</td>
</tr>
<tr>
<td>Boddy (2005)</td>
<td>pT1-3 $HIF1\alpha$, VEGF</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Movsas (2002)</td>
<td>cT1-3 $pO_2$</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>Carnell (2006)</td>
<td>cT1-3 Pimo</td>
<td>92%</td>
<td></td>
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<tr>
<td>Morton</td>
<td>High $pO_2$</td>
<td>67%</td>
<td>2.5</td>
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</table>
Hypoxia Confers Poor Outcome?

Early PMH Experience

Log-rank $p = 0.018$
(Median follow-up 20 months)

Oxic, n=72

Hypoxic, n=71

Years from RT completion

PSA-failure free
Androgen Withdrawal (Bicalutamide) Reduces Hypoxia in Patients

Significant reduction in hypoxia for all patients (p<0.005)

(Pre-Treatment pO₂ vs. Post-Treatment pO₂)
Multidisciplinary Strategy

Biologic Imaging

4D Imaging

Cervix Cancer

Lab

IMRT

Oxic, low IFP

Hypoxic, low IFP

Oxic, high IFP

Hypoxic, high IFP

Log-rank p = 0.0097

DFS

Time (y)

Pre-treatment IFP (mmHg)

Post-treatment IFP (mmHg)

ZD6126 treated

Control

Trendline (ZD6126)

Line of Identity (Control)
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- Lee Manchul
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- Fernanda Herrera
- Philip Chan
- Rob Dinniwell
- Barbara Bachtiary
- Karen Lim

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- Shirley Brown

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- Judy Quintos

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