The Management of Gynecologic Cancers: **Radiobiology**

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Overview of presentation

- Assessment of normal tissue response
- Radiobiology modeling
- Role of HPV in tumor response
- Hypoxic and tumor response

Radiobiology and normal tissue response and tolerance

- The Emami paper (*IJROBP* **21**: 109–122 1991)
  - 1/3, 2/3, whole organs - some clinical, some laboratory data
  - Consensus of clinical experience and opinions
  - Concerns with delivered dose and measurements of dose
  - ***Out of date***: Move from 2D to 3D treatment planning, higher energy beams, better penetration, improved ability to measure dose, increased use combined therapy
- Quantitative – QUANTEC, CTCAE v4.0, LENT-SOMA, IIEF
  - Quantitative Analysis of Normal Tissue Effects in the Clinic
  - Updated guidelines published in Red Journal
    - IJROBP vol 76, No., 3 2010 (suppl.) – 16 organ-specific papers
  - Radiation dose-volume effects of the urinary bladder
    - Viswanathan *et al*. *IJROBP* **76**: 3: S116–S122, 2010
- Cervix BRT: size of 60-Gy volume and dose rate have impact on late rectal complication

BED = Biologically ***Effective*** Dose

- **BED** commonly used for isoeffective dose calculations
- **BED** is a measure of the true ***biological*** dose delivered by a particular combination of ***dose per fraction*** and ***total dose*** to a particular tissue characterized by a specific **α/β ratio**

- **BED** is not Biologically ***Equivalent*** Dose

- Biologically ***equivalent*** doses are calculated in 2-Gy equivalents using the EQD2 equation
- Cumulative: brachytherapy dose added to the dose from external beam therapy

Bentzen *et al., Radiother Oncol* 105: 266–268, 2012
Dale, *Br J Radiol* 58: 515–528, 1985

Biologically Effective Dose (BED)

- BED compare effects fractionation schedules
  - need to know α/β ratio of the tissues concerned

$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right]$$

BED = total dose . [RE]

- with **n** number of fractions, **d** dose per fraction and **α/β** ratio
- for very low or very high doses per fraction concerns regarding the validity of the linear quadratic model, and concerns exist for α/β ratio for tumors (α/β =10)

External beam (EBRT) & brachytherapy (BT)

For combined schedules, calculate the total BED

$$BED_{tot} = \sum_i BED_i$$

This general BED expression does not take into account the proliferation during treatment could decrease as much as about 1 Gy/day

Beskow *et al. J Contemp Brachytherapy*. 2012 4(4):205-12

BED with proliferation during treatment

The effect of proliferation - supplementary term subtracted from BED*tot*

$$BED_{prolif} = \sum_i BED_i - \frac{ln(2)}{\alpha} \frac{T_{treat} - T_k}{T_p}$$

where ***Ttreat*** is the overall treatment time, ***Tk*** is the time for the onset of proliferation, ***Tp*** is the effective doubling time during proliferation and **α** is the linear parameter of LQ model.

Thus, the repopulation time **Tp** describes the proliferation of tumors after damage has been inflicted through treatment.

The actual time available for accelerated repopulation is ***Ttreat*** – ***Tk*** *and* no correction for proliferation is needed if the overall treatment time is shorter than **Tk**.

External beam (EBRT) & brachytherapy (BT)

$$BED_{EBRT} = nd\left\{1+\frac{d}{\alpha/\beta}\right\}$$

$$BED_{BT} = D\left\{1+\frac{2D}{(\alpha/\beta)\,\mu T}\left[1-\frac{1}{\mu T}(1-e^{-\mu T})\right]\right\}$$

low-dose rate with ***significant repair of damage during delivery***

where *D* is the radiation dose, *T* is the duration of the BT session and μ is a parameter characterizing the repair of sublethal damage in the irradiated tissues; $\mu = ln(2)/T_{1/2}$, where $T_{1/2}$ is half-life of sublethal damage repair

BED example

- Treatment consists of 50 Gy in 25 fractions followed by 15 Gy in three fractions over 5 days. Assuming that the α/β ratio is 2 Gy

$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right]$$

- the total BED=
- $50(1 + 2/2) + 15(1 + 5/2) = 152.5\ \mathrm{Gy}_2$

The B***effective***D is further reported as ***equivalent*** dose in 2 Gy per fraction, EQD2

By definition, $BED = \text{total dose} \times RE$

it follows that, $\text{total dose} = BED / RE$

$$RE = (1 + d / [\alpha/\beta])$$

Therefore, an equivalent total dose in 2-Gy fractions (EDQ2) can be found for *any* BED by dividing the BED by the RE for 2-Gy fractions, using the appropriate **α/β** ratio

Fowler, *IJROBP* **73**: 5, 1532–1537, 2009

BED example ***as EQD2***

- Treatment consists of 50 Gy in 25 fractions followed by 15 Gy in three fractions over 5 days. Assuming that the α/β ratio is 2 Gy

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

- EQD2 = 152.5/(1 + 2/2) = 76.3 Gy
- Which is an equivalent dose close to 76 Gy delivered in 38 x 2Gy fractions

BED to EQD2

- A more practical alternative is to convert the BED values to equivalent total doses delivered in 2 Gy fractions
  - more practical to clinical practice
  - more familiar to clinicians
  - interpreted according to clinical experience
- Easier to understand than BED, but difference should not be exaggerated

$$\mathrm{BED} = nd\left[1 + \frac{\mathrm{d}}{\alpha/\beta}\right]$$

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

The B***effective***D is further reported as ***equivalent*** dose in 2 Gy per fraction, EQD2

Isoeffect formula – Withers formula

$$EQD_2 = D\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

No change in overall treatment time and incomplete repair negligible

Comparison with previous reports

$$EQD_2 = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

Tumor **α/β**=10 divide BED in Gy_{10} by (1 + 2/**10**) = 1.2

Normal **α/β**=3 divide BED in Gy_3 by (1 + 2/**3**) = 1.667

Breaks: Joiner, *IJROBP* **58**:3 871-5 2004

Brachytherapy - BED

- Proliferation between EBRT and BT
- Doses to normal tissues are generally lower than doses to tumor tissues
  - apply a dose modifying factor (DMF)

$$D_{\mathrm{Eq}} = \frac{\left(n_{\mathrm{Ext}} * d_{\mathrm{Ext}} * \left[1 + \left(\frac{d_{\mathrm{Ext}}}{(\alpha/\beta)}\right)\right]\right) + \left(n_{\mathrm{HDR}} * d_{\mathrm{HDR}} * \mathrm{DMF}_{\mathrm{HDR}} * \left[1 + \left(\frac{d_{\mathrm{HDR}} * \mathrm{DMF}_{\mathrm{HDR}}}{(\alpha/\beta)}\right)\right]\right)}{\left(1 + \frac{\mathrm{d}_{\mathrm{REF}}}{\alpha/\beta}\right)}$$

- Orton (1997) BED values, Barton (1995) EQD2 values [EBRT]

Nag and Gupta IJROBP 46: 2, 507–513, 2000

Brachytherapy

- The recommended mean combined EBRT plus brachytherapy, EQD2 was
  - 78.9 Gy [SD=10.7] for Stage IB–IIA patients
  - 83.3 Gy [SD=11.2] for Stage IIB–IVA patients
- For all stages, EBRT plus brachytherapy
  - 80.9 Gy [SD=10.14].

Viswanathan AN, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1):250-5.

BED limitations

- need to know α/β ratio
- LQ fails at extremes of low dose rate and large fraction sizes
- Hot spots of treatment
- Previous cytotoxic chemotherapy
- Previous surgery
- Extremes of age
- Vascular pathology
- Breaks in treatment, compensation for accelerated proliferation
- Generic values of 10 Gy for tumors and 3 Gy for normal

Biomarkers of response in cervical cancer

- Tumor radiosensitivity (tumor biopsy and lymphocytes)
  - SF2 predictor of response (Cathy West)
- Early and late side effects (lymphocytes) (Anna Padjas)
  - No simple correlation between radiosensitivity
- Review the prognostic and predictive significance of biomarkers in cervical cancer[1]
  - recurrence after RT, SUV on FDG-PET scans and intra-tumoral oxygen levels
- Markers associated with poor prognosis[2]
  - Microarray and miRNA
  - VEGR, EGFR signaling (EGFR and C-erbB-2) [therapy]
  - carbonic anhydrase 9 (CA-IX) and HIF-1α [hypoxia]
  - Immune response, COX-2 and serum SCC-antigen

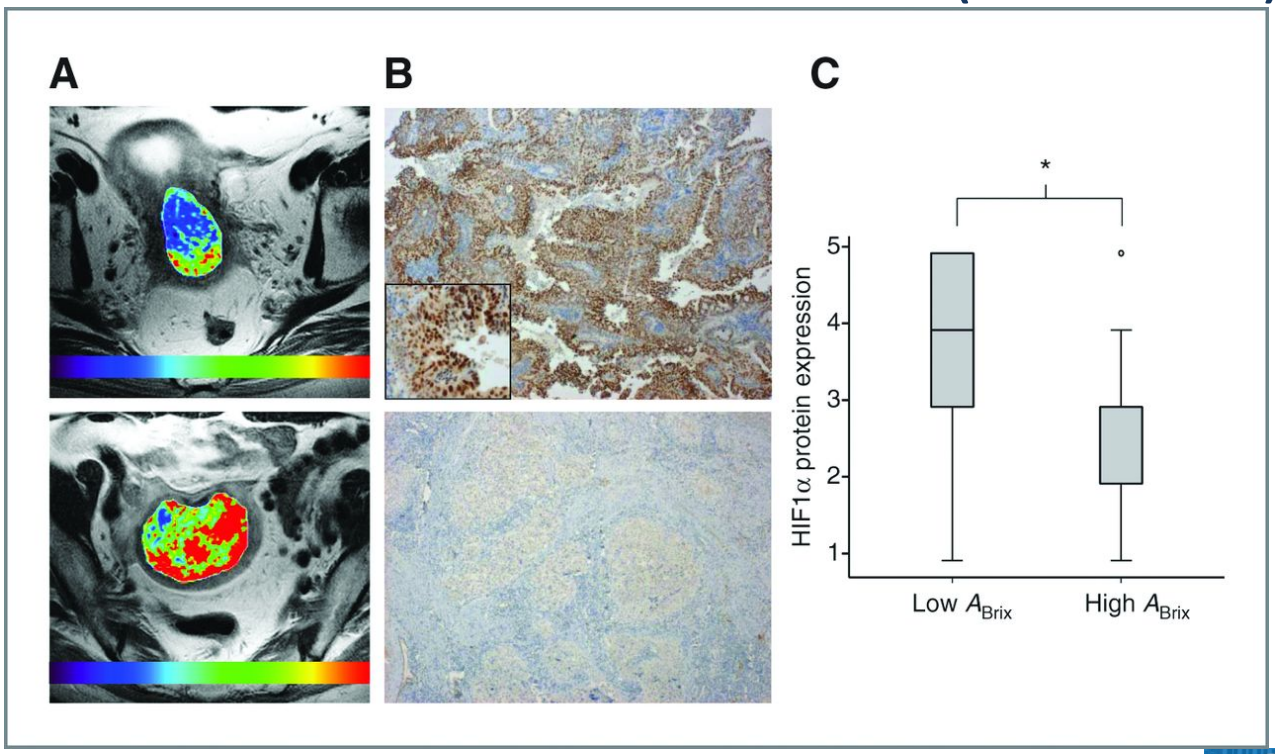
1. Kloop and Eifel, Semin Radiat Oncol 22:143-150 2012
2. Noordhuis , IJROBP, Vol. 79, No. 2, pp. 325–334, 2011

Tumor hypoxia

- Association has been detected between tumor hypoxia and unfavorable clinical outcome in cervical carcinoma
  - Hockel et al. [Can. Res 1999] unfavorable outcome was mainly due to loco-regional failures
- Disadvantages of direct pO_2 measurements are operator dependency and the invasive nature – lactate levels, CA-IX, HIF1, GLUT1
  - High CA-IX expression significantly correlated with tumor size (p = 0.003) and depth of cervical invasion (p = 0.028), an independent predictor of poor survival [Laio et al Gyn. Onc 2010]
- Non-invasive method needed

Hypoxia and cervical cancer

- Patients with hypoxic tumors have significantly worse disease-free and overall survival
- Hypoxia-Induced Gene Expression Revealed by Dynamic Contrast-Enhanced MRI (DCE-MRI)



Halle *et al.* Cancer Res; 72(20) October 15, 2012

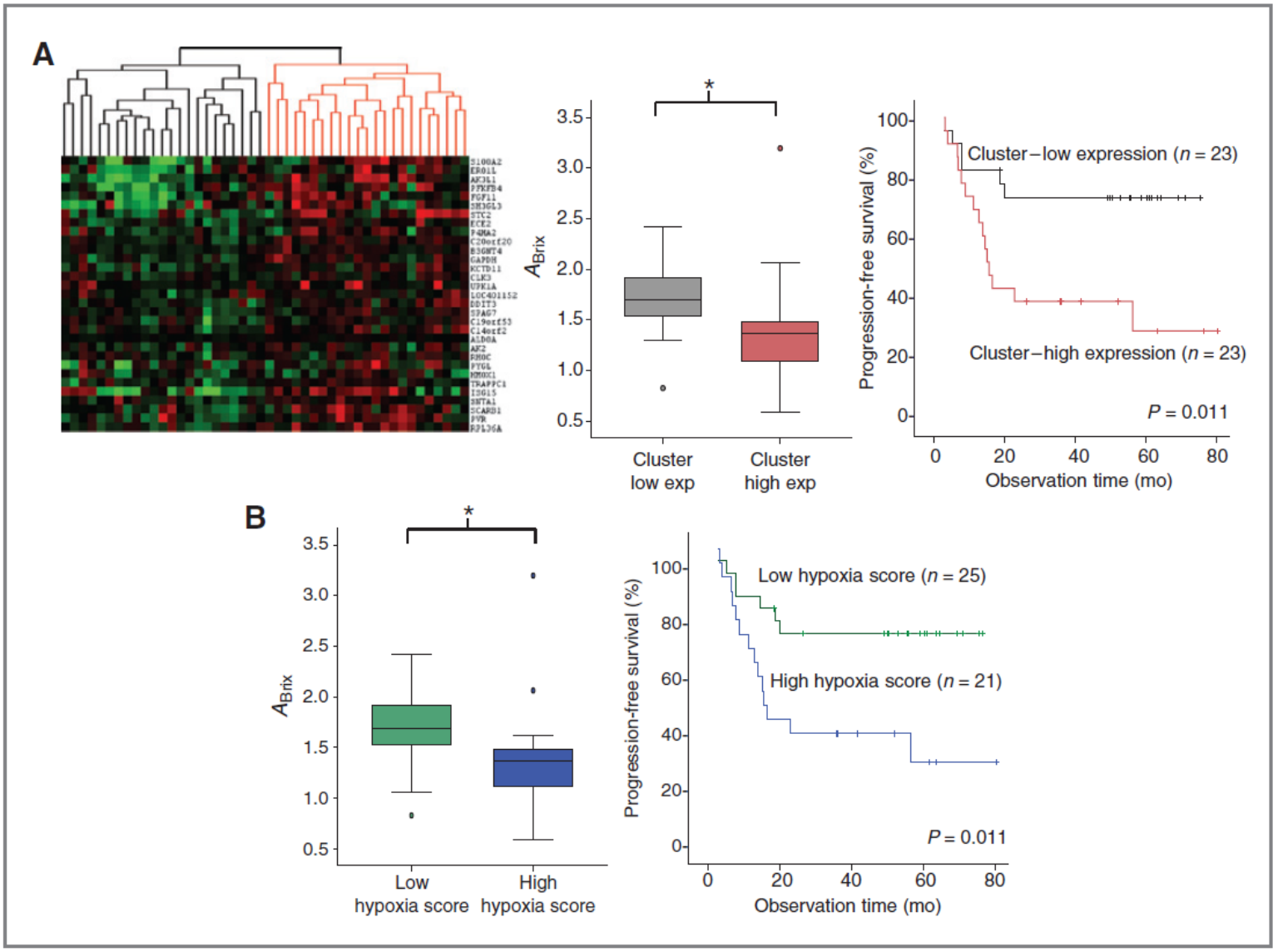


Figure 3. The DCE-MRI hypoxia gene signature in relation to A_{Brix} and clinical outcome. A, hierarchical clustering of the 46 cervical cancer patients with both DCE-MRI and gene expression data based on expression of the 31 genes in the DCE-MRI hypoxia gene signature (left). Box plot of A_{Brix} (middle) and Kaplan-Meier curves for progression-free survival (right) of patients in the low (black) and high (red) expression cluster. B, box plot of A_{Brix} (left) and Kaplan-Meier curves for progression-free survival (right) of patients with low (green) and high (blue) DCE-MRI hypoxia score. The box plots show median, first, and third quartile; the whiskers extend to the farthest points that are not outliers. $^*P < 0.01$ (Mann–Whitney U test). P values from log-rank test and number of patients are indicated in the Kaplan-Meier plots.

Halle *et al.* Cancer Res; 72(20) October 15, 2012

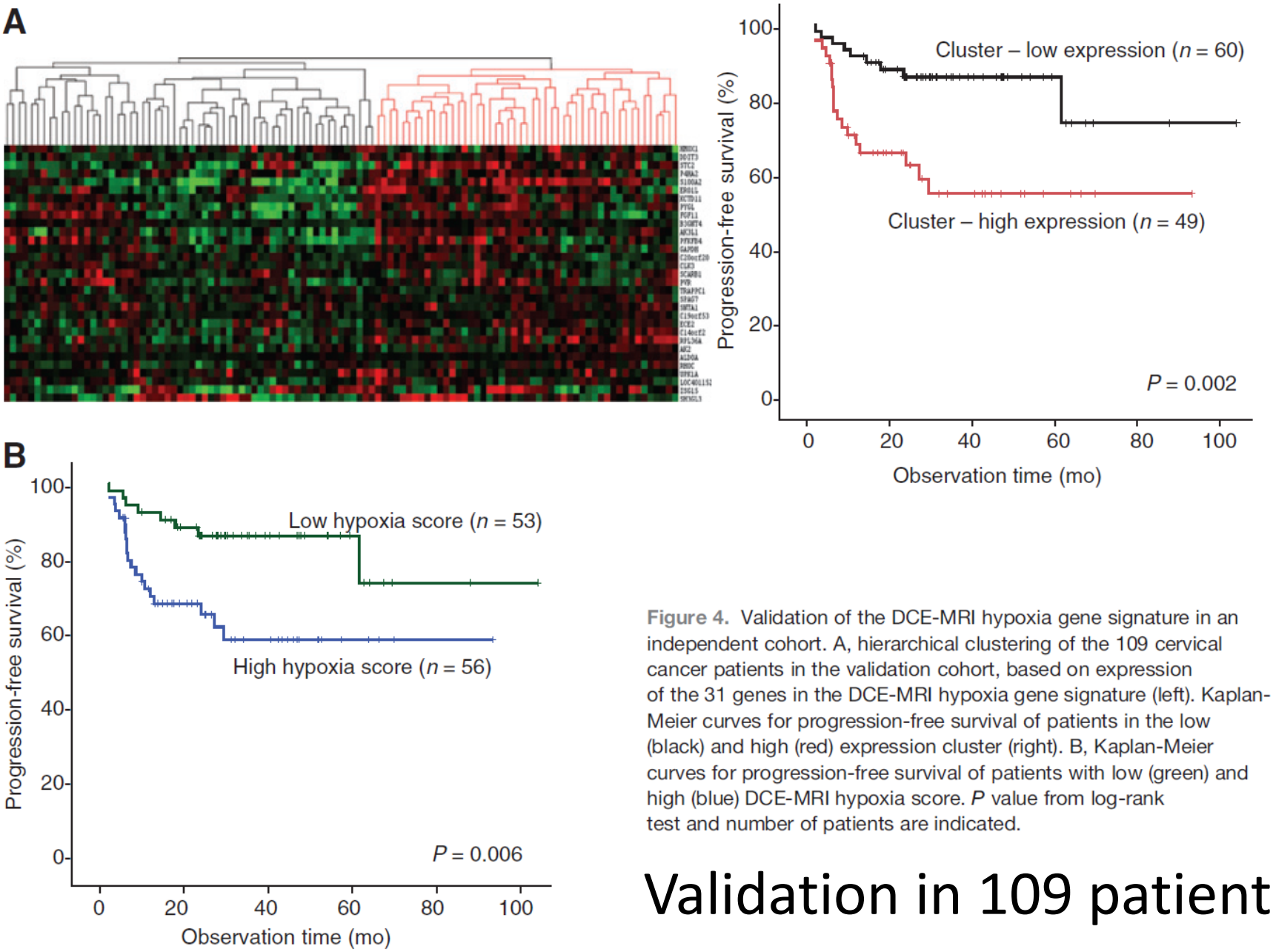


Figure 4. Validation of the DCE-MRI hypoxia gene signature in an independent cohort. A, hierarchical clustering of the 109 cervical cancer patients in the validation cohort, based on expression of the 31 genes in the DCE-MRI hypoxia gene signature (left). Kaplan-Meier curves for progression-free survival of patients in the low (black) and high (red) expression cluster (right). B, Kaplan-Meier curves for progression-free survival of patients with low (green) and high (blue) DCE-MRI hypoxia score. *P* value from log-rank test and number of patients are indicated.

Validation in 109 patients

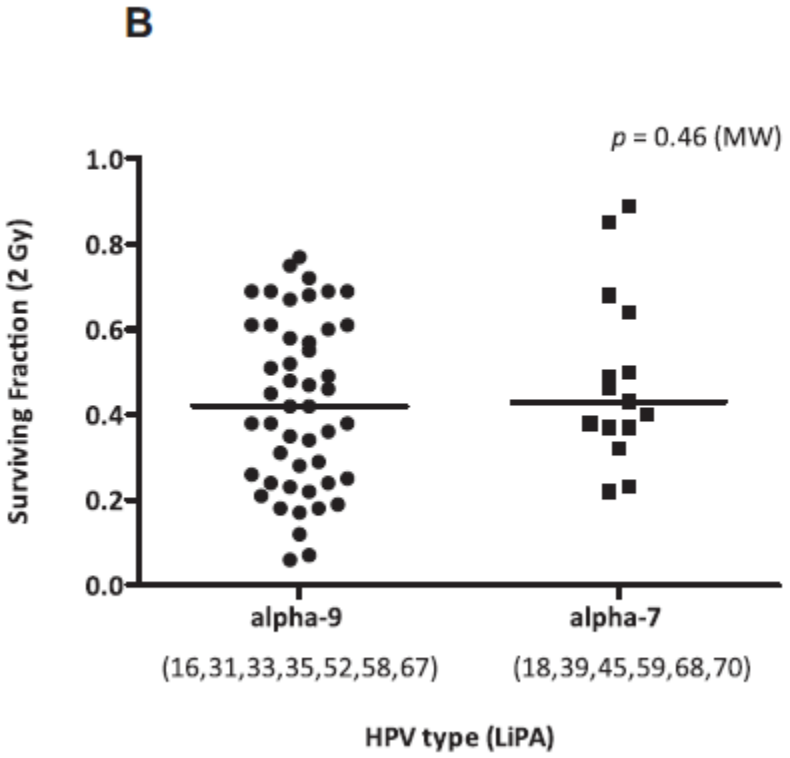
Halle *et al.* Cancer Res; 72(20) October 15, 2012

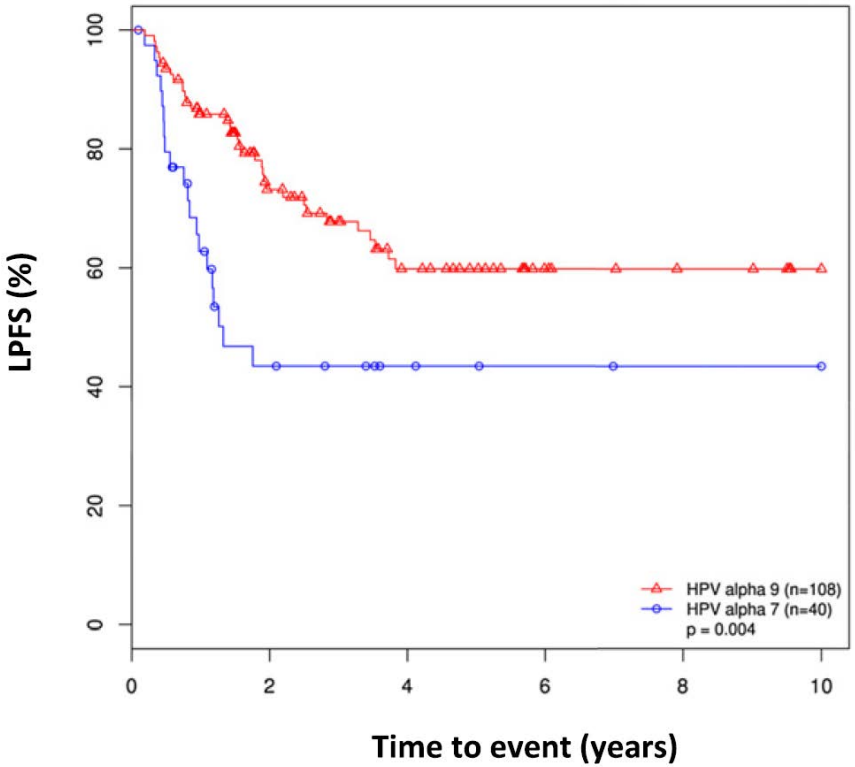
HPV and cervical cancer

- E6 and E7 degradation and/or inactivation of p53 and Rb proteins – p21 regulation
- HPV type 18: association with poor prognosis in early stage[1]
- HPV genotype distribution in low-grade cervical lesions[2]:
  - HPV16 was 2-fold and HPV18 was 1.5-fold more common in SCC than in HPV-positive LSIL; HPV18 most common in USA
- HPV genotypes predict survival benefits from primary RT[3]
  - prognostic value of different HPV genotypes: HPV18 and HPV16
  - Two high-risk HPV species: **alpha-7** (HPV18, 39, 45) and **alpha-9** (HPV16, 31, 33, 52, 58)
- Concurrent Chemotherapy and Radiation Therapy[4]
  - A significant improvement in disease-specific survival
    - HPV18-positive (P=0.019) and HPV58-positive (P=0.026) CCRT patients compared with the RT alone group

1. Burger *et al*. *J Natl Cancer Inst*. 1996 Oct 2;88(19):1361-8.
2. Clifford *et al*. *Cancer Epidemiol Biomarkers Prev*. 2005 May;14(5):1157-64.
3. Wang *et al.* IJROBP 78: 1111–1120, 2010
4. Wang *et al*. IJROBP 84: No. 4, pp. e499-e506, 2012

Intrinsic radiosensitivity does not account for the difference in response after radiation therapy HPVα**7** and HPVα**9** (Cathy West group)





Hall et al. IJROBP 85: 5, e223–e229 (2013)

Prognostic significance of human papillomavirus (HPV) α 9 and HPVα7 in cervix carcinoma patients who received radiation therapy alone with curative intent.

REVIEW: Vozenin *et al.* Cancer Treat Rev. 2010 36(8):629-36

Immune response and cervical cancer

- Human leukocyte antigen E (HLA-E), a non-classical HLA class Ib molecule, plays an important role in immune surveillance and immune escape of virally infected cells
  - High HLA-E expression in cervical adenocarcinomas was associated with favorable long term disease-specific and recurrence-free survival (P = 0.005 and P = 0.001, respectively).

But not cervical squamous cell carcinomas (SCC) cervical adenosquamous carcinomas (ASC)

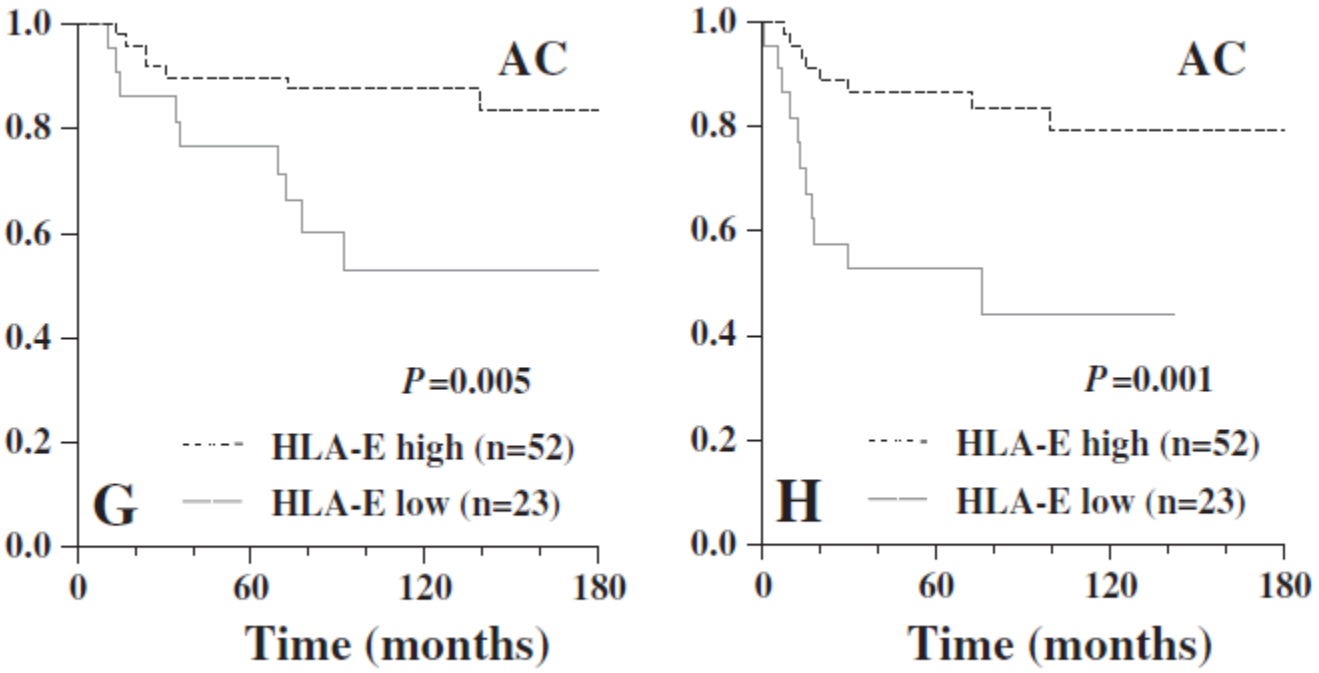


Figure 2 Disease-specific and recurrence-free survival curves.

Spaans *et al*. Journal of Translational Medicine 2012, 10:184

Microarray and microRNA

- Smaller studies with large number of genes
  - Few patients, tumor biopsy samples
- microRNA are small non-coding ss RNAs that regulate gene expression
  - Several miRNA dysregulated in cervical cancer
  - miRNA associated with HPV status (miR-218)
  - proliferation, migrations and invasion (miR-372)
- Predictor of response to therapy or a novel target of therapy –VEGF, EGFR, mTOR, HDACs

Hu X, et al., Cancer Res. **15**;70(4):1441-8 2010
Zagouri *et al, Gynecol Oncol*. 2012 **126**(2):291-303 2012
Suh *et al, J Gynecol Oncol*. **24**(1):66-82 2013

Conclusions

- Adopt EQD2 modeling
- Results remain mixed with regard to the predictive value
  - Single gene and tissue biomarkers
  - Multi gene and tissue biomarkers show promise
  - VEGF, COX-2, hypoxia, microRNA
- Standardizing methodology for scoring immunohistochemical findings
  - Disparate array of potential markers
- Identify patients at low risk of recurrence for dose de-escalation and bio-molecular targeting