

Disclosures

- Roche
- Pfizer

The Oncologist dream -The ability to predict response

- From tumour tissue
- Normal tissue
- Blood
- Plasma

Because in practice as radiation oncologist I observe huge variability in outcome (response and normal tissue damage)

Definition of a bio marker

Biomarkers are indicators of normal, pathological processes and pharmacological or RT responses

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    graph TD
      A[Definition of a bio marker] --> B[Predictive of the chance of response to a particular treatment]
      A --> C[Prognostic of risk of developing a disease, the chance of spread, the aggressiveness and the chance of survival]
    
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Predictive biomarkers in CRC

- TS, Tp, DPD
- Topo-1
- ERCC1
- Kras/Braf (PTEN, PI3K)
- Amphiregulin/Epiregulin
- P53
- Ki67
- MSI
- Cyclin D etc.....

The ideal future for rectal cancer

=

The DODO

Factors associated with limited response to CRT

- Poorly diff (G3)
- Circumferential extension > 2.5mm on ERUS

(Fixed tumours)
(Metastatic disease)

- ie Different biology ?

Lin AY et al Int J Colorect Dis 2008;23:243-46

Biomarkers -Challenges that face us (1)

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- We are limited to the characteristics of the cancer itself (ignores the micro-environment)
- We are limited to the characteristics of the primary cancer

We are limited to information on the primary tumour

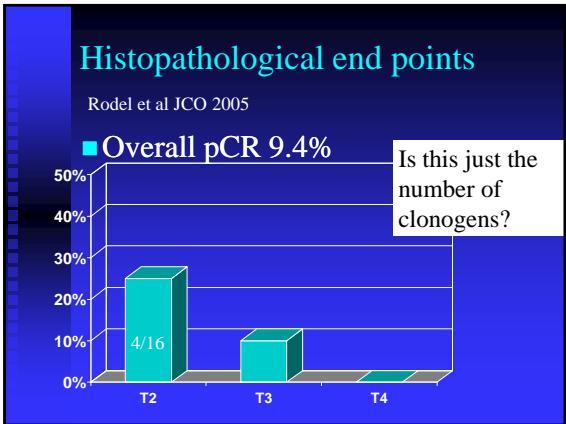
- only have information on the biological activity of the primary tumour and not the mesorectal and pelvic lymph nodes. These may well respond differently (Bujko 2004, Negri BJC 2008)

Challenges that face us (1)

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- We are limited to the characteristics of the primary cancer
- We are limited to the characteristics of a small % of the primary cancer

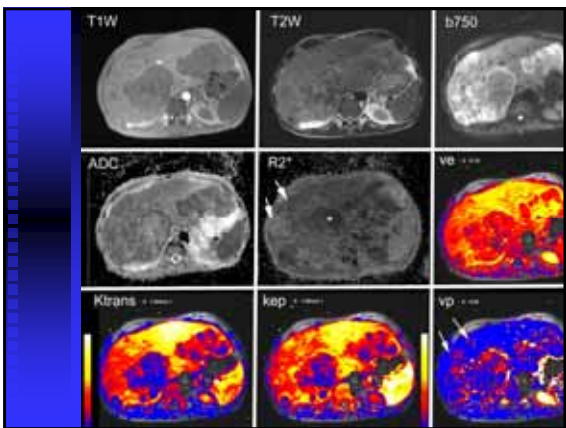
Challenges that face us (1)

- We are limited to the characteristics of the cancer itself (ignores the micro-environment)
- We are limited to the characteristics of the primary cancer
- We are limited to the characteristics of a small % of the primary cancer
- We are limited to a more advanced stage –does that matter?



conclusion

- Accurate predictions of response less likely - more likely to predict resistance



Challenges that face us (2)

- We are limited by observer error in scoring IHC rather than a mutation at codons 12 13 being present or not

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- We are limited by the complexity of integrating cytotoxic chemotherapy agents and radiotherapy (different schedules often not systemically active doses)

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- We are limited further by the even greater complexity of integrating biologicals into CT and RT combinations
- We are limited by being more successful at predicting major resistance to cytotoxic chemotherapy agents and radiotherapy.

Challenges that face us (3)

- We are limited by the validity of the statistical analysis.
- We are limited by 'overfitting' . .
- We are limited by bias in terms of systematic erroneous associations
- We are limited by a lack of reproducibility
- We are limited by the lack of commercial availability

Overfitting

- Large numbers of potential genes in a multivariate analysis
- By chance some will appear significant
- Often hypothesis cant be replicated by other groups

Needs validation in very large independent dataset

Cetuximab CRT studies in rectal cancer

	no	2 nd drug	RT Gy/#	pCR
Chung 2006	20		50.4/28#	2/20 10%
Machiels 2007	40		45/25#	2/40 5%
Rodel	48	Oxaliplatin	50.4/28#	4/48 9%
Hoffheinz	20		50.4/28#	5/20 25%
Horisberger 2009	50		50.4/28#	4/50 8%
Bertolini 2008	40		50/25#	3/40 7.5%
Hong 2007	10	Irinotecan	50.4/28#	2/10 20%

Overall pCR rate

$22/228 = 9.7\%$

Conclusions

- Don't oversimplify- it is complex
- Processes/ pathways rather than single steps
- We need reliable reproducible tests
- Technologies and statistical methods need refining
- We need validation in large studies
- More likely to have negative predictions/markers for resistance

