Evidence-based medicine and new technology
Aims

Outline the concepts of evidence based medicine (EBM) as applied to new technology and external influences on EBM to be able to analyse the quality of evidence.
Learning objectives

- Explain the need for EBM
- Define the grading of evidence
- Give examples for the need for EBM
- Define the terminology of study phases as applied to radiotherapy and give examples
- Explain the factors which influence EBM with examples
Cascade of EBM fed by scientific discoveries and technological advances with the ultimate aim of improving the outcome of medical interventions of importance to the patient and population.
Describe the grading consensus; mention some difficulties – high grade does not always equate with high quality.

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Evidence based medicine

- STRENGTH OF RECOMMENDATION:
  - A. At least one randomised controlled trial as part of a body of literature of overall
good quality and consistency
  (Evidence levels Ia, Ib).
  
  - B. Well conducted clinical studies but no randomised clinical trials.
  (Evidence levels IIa, IIb, III).
  
  - C. Expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.
  (Evidence level IV).

Levels of evidence may come with recommendations for practice. The strength of these recommendation depends on the evidence available.
Evidence based medicine

Example of brain metastases

Use the example of evolution of RT technology in the treatment of brain metastases
**Oncological management options**

**Brain metastases**

- **Local therapies**
  - surgery
  - radiosurgery
  - radiotherapy

- **Systemic therapies**
  - chemotherapy
  - targeted therapy

- **Supportive care**

List of treatment option in the management of patients with brain metastases – RT techniques are local as opposed to systemic treatments. If time make it clear that all patients with brain mets should receive supportive care. Further discussion will centre on radiotherapy techniques.
Conventional treatment is whole brain radiotherapy. Radiosurgery as localised treatment of individual metastases has been practiced for over 30 years – what is the evidence of benefit?
These data were presented at the first stereotactic radiosurgery conference and would seem to demonstrate almost magical effectiveness of radiosurgery. Point out that the endpoint of “control” has no defined meaning and is particularly unhelpful without information on time. e.g is it just imaging control and is it 1 day, 1 month or 6 months after treatment?

### Radiosurgery for brain metastases

#### early results in 1993

<table>
<thead>
<tr>
<th>Centre</th>
<th>no.patients</th>
<th>median FU (months)</th>
<th>control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston</td>
<td>217</td>
<td>11</td>
<td>88%</td>
</tr>
<tr>
<td>Stockholm</td>
<td>200+</td>
<td>-</td>
<td>94%</td>
</tr>
<tr>
<td>Pittsburgh+</td>
<td>116</td>
<td>9</td>
<td>83%</td>
</tr>
<tr>
<td>Cologne+</td>
<td>28</td>
<td>3</td>
<td>93%</td>
</tr>
</tbody>
</table>

Abstracts from 1st Congress of Stereotactic Radiosurgery Society
Stockholm June 1993
The best way of presenting local control data is in actuarial manner which includes information on the number of patients and the length of follow up. The results of the first 30 patients are shown – might be 90% at 2-3 months but it drops rapidly.
Survival is probably a more important endpoint and the first cohort shows a median survival of about a year.
As is the usual case in studies of new technology or any novel approach, with time the results become less good and the median survival a couple of years later after more patients had been accrued dropped to 6 months.
Oncological management options

Brain metastases: example of evidence based medicine

Is the evidence sufficient to introduce radiosurgery as the treatment of choice

- radiosurgery
- radiotherapy

- Systemic therapies
  - chemotherapy
  - targeted therapy

- Supportive care

Pose this question. What is the level of evidence and what is your grade of recommendation
Answer is in the list well known to anyone involved in the evaluation of new treatment approaches – confounding factors which influence outcome in single arm studies – can dwell on individual issues time permitting.
Testing new technology should follow the drug testing paradigm.

Evidence based medicine

Conventional design to evaluate

Phase I

Phase II

Phase III

model of drug testing
Explain meaning of phase I with drugs.

Phase I drug trial is the first time of exposure to man. It focuses on drug safety and pharmacology namely pharmacokinetics and pharmacodynamics. The aim of Phase 1 trial is to obtain the Maximum Tolerated Dose (MTD) which is the dose to be used in Phase II trials.
With new technology Phase I should focus on feasibility and toxicity. Phase I drug trials typically may take all types of cancers in patients without standard options.

Consider CHART trial where the dose was slowly escalated to 54Gy as deemed tolerable.
Explain Phase II design and the issues (to be discussed later)

Phase II drug trials uses the MTD from Phase I trials. It is meant to evaluate efficacy in a standard cohort of patients. The number of patients in phase II trials are small and have rigid criteria for disease. Usually they tend to be fitter patients with good organ function.
The issues with phase II of new technology are the same – shown in the previous example of brain metastases; now demonstrated in more detail.
Principal determinant of outcome in any study is patient selection – this simply shows the effect of prognostic factors on survival in patients with brain metastases treated with radiosurgery – so in any of the phase II studies shown previously the selection of patients would have been principally responsible for the survival outcome (nothing to do with treatment technology)
Demonstrate the effect of changing practice on outcome here demonstrated as change in the method of staging; each group improves simply due to changes in staging (Will Rogers phenomena).

Original quote: When the Oakies left Oklahoma and moved to California, it raised the I.Q. of both states.

Oklahoma – Smart
California – Stupid
Oregon – Intermediate

By more extensive staging, we are able to find patient with minimum disease and upstage them. Eg. PET CT may find micro metastases and up-stage a patient from Stage II to stage IV. However this patient is likely to be fitter and have smaller disease burden.
Hence the need for randomised studies which is the only way of convincingly demonstrating comparative efficacy – i.e. is the new treatment better than the old and this also applies to technology.
Radiosurgery for multiple brain metastases

few brain metastases

randomise

- whole brain radiotherapy
- whole brain radiotherapy & radiosurgery

WBRT  whole brain radiotherapy
SRS   stereotactic radiosurgery

Show on example of the efficacy of radiosurgery – the slides are self explanatory – based on publication by Andrews et al 2004 (RTOG study)
Few = 1-3 brain mets, biggest 4 cm, others <3cm
333 entered, 2 excluded.

There was no difference in the overall survival of the 2 groups.
Radiosurgery for multiple brain metastases

RTOG trial 9508

Survival – patients with multiple brain mets

Survival (%) vs Time (months)

p=0.978

WBRT alone

WBRT + SRS

WBRT whole brain radiotherapy
SRS stereotactic radiosurgery

Andrews et al 2004
Patients were stratified to either single or 2-3 mets.
There was a 6 week improvement in MST for patients receiving radiosurgery.
No difference was seen between treatment machines.
Conclude – grade I evidence that radiosurgery prolongs survival in patients with solitary brain metastases and has no influence on survival (in addition to whole brain RT) in patients with multiple brain metastases. Yet this technique is not infrequently offered to patients with multiple brain mets. I call it “triumph of marketing over evidence based medicine.”
Determinants of clinical practice

Science → Evidence Based Medicine

Technological → Evidence Based Medicine

Implementation

→

Improved clinical outcome
Evidence based medicine

Randomised controlled trial
(Phase III trial)

Cornerstone of evidence based medicine
The question posed is how robust and trustworthy the “cornerstone” is. The following slides explain the sequence of development and implementation of randomised trials and the factors which may influence it.

Starting with design as a bad trial design will not yield satisfactory results.
Evidence based medicine

Choice of trial

Trial design

Randomised controlled trial (Phase III trial)

Reporting of trial

Implementation

Impact on healthcare

Ending up in implementation
We can’t do all the trials we want. So what influences the choice of trial? Following slides are self explanatory.
Evidence based medicine

Choice of trial

Which tumour type?

Randomised controlled trial
(Phase III trial)

Reporting of trial

Implementation

Impact on healthcare
The choice of trial should be based on need – so most research activity should be in lung cancer (commonest cause of cancer death). The trials should be centre on common cancers and those with highest morbidity eg DCIS less important than lung cancer.
If we use the number of charities supporting the different tumour categories as a surrogate measure of research support and the choice of trial we see that this is not based on “population need”.
The poor public (and possibly government) interest may have something to do with the equivalent of “social class distribution” and therefore the political influence of the affected population.
Choice of trial

Which tumour type?

Randomised controlled trial (Phase III trial)

Reporting of trial

Implementation

Impact on healthcare

So choice of trial is not necessarily governed by need.
Evidence based medicine

Choice of trial

Which tumour type?

Randomised controlled trial
(Phase III trial)

Which aspects of treatment and care are subject to evidence based medicine?

Implementation

Impact on healthcare

Self explanatory
Developments in oncology

Radiotherapy
  sensitizers
  fractionation
  technology
Systemic therapy
  chemotherapy
  targeted agents

All these aspects can be tested; is the choice of therapy to be tested based on predicted efficacy?
Self explanatory. Much of these are drug related trials
If we were to consider an important aspect of radiotherapy such as altered fractionation.
Radiotherapy in NSCLC

Randomised trial of CHART

Continuous Hyperfractionated Accelerated RadioTherapy (CHART) 54Gy 36 fract’s in 12 days

Conventional radiotherapy 60Gy 30 fract’s in 6 weeks

Showing the efficacy of altered fractionation of RT with CHART
This trial demonstrated a 22% reduction in deaths with CHART compared to conventional radiotherapy.
Very effective yet in terms of publication as a measure of research activity – poorly researched. How does this compare to other treatments?
When we consider systemic therapy then the picture is different.
Chose just one drug – self explanatory

For any new drug, initially there is a rapid increase in the number of publication but the actual number of phase III trials are small. After a peak, (here at 10 years – maybe at the end of patent) then the number of publication rapidly diminishes.
Gemcitabine in NSCLC

Annual publications as a measure of research activity

21 randomised trials including Gemcitabine (7135 patients)

3 show survival benefit for one regimen
18 show no survival difference between regimens

Gonsalves - Medline search
Developments in oncology

Radiotherapy
sensitizers
fractionation
technology
Systemic therapy
chemotherapy
targeted agents
A similar story is seen with targeted therapies eg gefitinib.
Using the same scale – this highlights the comparison
Evidence based medicine

Choice of trial

Which tumour type?

Randomised controlled trial
(Phase III trial)

Which aspects of treatment and care are subject to evidence based medicine?

Implementation

Impact on healthcare
There are many different pressures apart from medical, for the choice of disease and treatment to be investigated.
What influences the core of the randomised trial?
The uncertainty principle and industry-sponsored research

B Djulbegovic et al 2000 Lancet, 356, 635-38

This paper was evaluating therapeutic studies on patients with myeloma.
Overall there was no difference in the distribution of preference for standard or innovative therapy.
Demonstrates equipoise in trials funded by non-profit organisations but clear lack of it in commercially sponsored trials which suggest bias. This is most likely explained by the selection of controls.
So even the heart of EBM is not without potential bias
Describe the process of licensing of new drugs and how this applies to new technology.
EMEA and FDA requirements for new drug therapies include pre-clinical (lab) and clinical data.
Licensing of new equipment

Regulatory authority requirements

- pre-clinical investigations
- pharmacology
- safety
- activity
  - in a specific indication

Technology requirements – see next slide. Is it the same??
Technology requirements before introduction into clinical practice. Only safety data is needed.
Evidence based medicine

Choice of trial

Trial design

Randomised controlled trial (Phase III trial)

Reporting of trial

Implementation

Impact on healthcare
Example of introduction of gamma knife.

Number of publications as a measure of activity/interest
Despite the large number of publications, there are virtually no randomised trials – of the 2 only one is acceptable quality (the trial in brain mets shown before)
Sometimes the argument is that the new therapy is so good that it is unethical to do trials comparing with standard therapy. In the case of breast cancer, a publication by WP Peters et al indicated much improved survival in breast cancer patients with high dose chemotherapy. Due to pressure from various groups, this treatment was supported by insurance companies. Many years later when clinical trial were completed, there was no evidence of an advantage of high dose chemotherapy.
Self explanatory. Tendency for publication of positive versus negative trial Eg GOG 111 was a positive trail indicating advantage for paclitaxel in ovarian cancer and published in NEMJ in 1996. GOG 112 was a “Negative” trial presented in abstract form and never published.
Time permitting show the complex relationship in healthcare; effect of funding, political influence etc. Of course the patients too have a strong influence on what may be provided by healthcare providers eg high dose chemotherapy for breast cancer.
The implementation is often described in guidelines but when tested it seems that actual implementation has not that much to do with guidelines but other influences, particularly economic – next slide
Again in the implementation depends partly on evidence and partly on other pressure. Economic pressure may be measure as what is cost-effective therapy (vs “cheap”) and many countries have set a limit of cost effectiveness per QALYs (Quality Adjusted Life Year saved).
Summarise what had been said
Determinants of clinical practice

- Science and technology
- Patient population
- Political, social and economic changes

Point out that clinical practice is only in part determined by evidence based medicine (as flawed as it might be) – these influences are possibly stronger.
Summary the highest level of evidence should be used to evaluate new therapies and new technologies in medicine.