

# Evidence-based practice in oncology, when it suits us?

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Oncology has a strong grounding in science. In radiation oncology, we have harnessed amazing technological advances resulting in the current state of the art linear accelerator producing high energy photon beams and incorporating an inbuilt CT scanning facility. It is driven by complex software and the derivation of radiation dose distributions results from ever more sophisticated algorithms enabling rotating arcs using beams with three dimensional fluctuations of dose within them. Alongside the engineering and physics, we have a long traditional in radiobiology exploring the interaction of radiation with biological systems, both tumours and normal tissues, to help us derive scientifically based radiation schedules to optimise outcome for patients.

Dissemination of our science is also highly developed. We have specialist journals, numerous teaching courses, nationally and internationally, conferences both virtual and live and in the social media sphere chat rooms and blogs to facilitate discussion and controversy. We are taught about the hierarchies of evidence with the randomised controlled trial and meta-analysis of these at the pinnacle, Level one evidence. National and international agencies promote and fund phase three trials as does the pharmaceutical industry to feed our quest for high level evidence. These trials are carried out with ever increasing rigour and sophisticated statistical design and analysis.

In contrast, the clinical practice of radiotherapy remains variable and idiosyncratic either ignoring or choosing to reinterpret high level evidence and clinical guidelines. The radiotherapy literature is littered with randomised controlled trials which have shown advantage to interventions which have never been adopted by the community. Examples are shown in [table 1](#). Too often our judgement is clouded by the challenges of changing practice. Two prime examples are first the use of continuous hyperfractionated

radiotherapy<sup>1</sup> which required a major reorganisation of the working day in a radiotherapy department delivering treatment three times a day and continuing across weekends but with a reduced overall time of 12 days compared with 42 days or more, and the use of carbogen and nicotinamide as a radiosensitiser in the use of radiotherapy for muscle invasive bladder cancer.<sup>2,3</sup> This involves breathing a high oxygen gas mixture (carbogen) during delivery of radiation which while simple requires a change in the treatment pathway for radiotherapy delivery. Both approaches have been shown to offer a survival advantage in non-small cell lung cancer and muscle invasive bladder cancer respectively. They have been included in national and international guidelines but have never been widely adopted. In contrast the 'easier' and more familiar option of adding chemotherapy both in the neoadjuvant setting and as a radiosensitiser with radiation is widely used often with very little supporting evidence.

It is clear that clinical decisions in practice depend far more on credibility, familiarity, reinforcing prejudice and funding structures. We will readily adopt evidence which either supports what we already do or makes life even easier. Hence the success of the START trials of breast fractionation<sup>4</sup> which confirmed the safety and efficacy of 3 weeks radiotherapy following lumpectomy in breast cancer compared with the traditional 5 weeks and the CHiPP trial<sup>5</sup> which confirmed 4 weeks treatment to be as effective as 7.5 weeks in prostate cancer. It is however notable that while readily adopted in the UK strengthened by National Health Service commissioners' recognition of a cost saving, in many parts of the world justification for the longer fractionation has been sought citing different populations, risk factors and lack of mature data. Again reinforcing prejudice and maintaining the status quo dominates scientific evidence.

Perverse incentives for prolonged and more intensive treatment which are built



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**Table 1** Selected randomised clinical trials in clinical oncology which have failed to impact on routine practice

Trial name	Tumour site	Intervention	Impact
CHART <sup>1</sup>	NSCLC	Accelerated 12-day radiotherapy	Recommended in guidelines Never widely adopted
DAHANCA 5–85 <sup>13</sup>	Head and neck	Nimorazole radiosensitisation	Never widely adopted
BCON <sup>23</sup>	Bladder	Carbogen and nicotinamide with radiotherapy	<20 centres worldwide Never widely adopted
EORTC 22791 <sup>14</sup>	Oropharyngeal	Twice daily radiotherapy	Never widely adopted
Hyperthermia <sup>15</sup>	Cervix, ovary head and neck bladder, rectum sarcoma recurrent breast	Regional hyperthermia with radiotherapy or chemotherapy	In use in parts of Europe No UK centre
TARGIT <sup>16</sup>	Breast	Intraoperative radiotherapy	Yet to be widely adopted
Bone pain Meta-analysis <sup>17,18</sup>	Bone metastases	Single dose radiotherapy	<50% patients receive single doses

BCON, Bladder Carbogen Nicotinamide; CHART, continuous hyperfractionated radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer; NSCLC, non small cell lung cancer; TARGIT, targeted intraoperative radiotherapy.

into funding systems based on fee for item as opposed to fee for episode have long been recognised, but not addressed. In radiotherapy, a prime example has been seen in the management of painful bone metastases for which radiotherapy remains the treatment of choice. There is a considerable evidence base showing that single doses produce effective pain relief with no evidence for added benefit from more prolonged courses. National and international guidelines recommend the use of single doses and yet although their use has increased over the last decade still population reviews rarely identify more than 50% of patients receiving single dose radiotherapy for bone pain. Various attempts to justify this are given including the treatment of ‘radioresistant’ tumours, predicted long life expectancy, and fear of toxicity yet all of these have been disproved in the large randomised trial datasets as relevant to predicting response from a single or prolonged course of treatment. The one factor, however, which has been shown consistently to relate to practice in management of metastatic bone pain is the funding model<sup>6</sup>; reimbursement per fraction delivered makes it very difficult to switch practice to single doses.

Similar and perhaps even greater tension exists in the use of chemotherapy where not only healthcare systems but also the pharmaceutical industry has a financial incentive to maximise treatment episodes. A good example is that of adjuvant chemotherapy for colorectal cancer where the umbrella trials in the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) initiative compared three cycles with six cycles and identified patients who had no additional clinically significant benefit for the longer course treatment which had been established as the standard of care based on industry funded clinical trials.<sup>7</sup> Similarly six cycles of herceptin for breast cancer have been shown to be non-inferior to twelve cycles and yet this reduction has not been widely implemented despite level 1 evidence.<sup>8</sup>

So what happens to the rational science literate clinician when faced with a patient and a clinical decision. There have been many models proposed for decision making in medicine. They recognise that the clinician is processing and interpreting a considerable body of information about any one patient to formulate that decision. The clinical history will be a strong component of this supplemented by information from clinical examination and diagnostic tests; these will then be shaped by others evaluating uncertainties in what are often subjective interpretation of clinical findings and radiological data. There will also be input from the patient who will have preferences often based more on emotive and logistic considerations rather than scientific facts. Discussion at a multidisciplinary meeting may attempt to inform a decision implicating current guidelines but often the resultant decision is that of the dominant members rather than reasoned appraisal. We then hide behind ‘clinical reasoning’ as our own inherent bias comes to the fore based on credibility, familiarity and reinforcing prejudice. This is encapsulated by a quotation from Louis Pasteur<sup>9</sup>: ‘Physicians are inclined to engage in hasty generalisations. Possessing a natural or acquired distinction, endowed with a quick intelligence, an elegant and facile conversation ..... The more eminent they are .... the less leisure they have for investigative work.....Eager for knowledge ....they are apt to accept too readily attractive but inadequately proven theories.’

Recognising the strength of our scientific base and our weakness in applying it to everyday clinical practice what is the solution? It is a disturbing fact that less than 50% of positive clinical trial outcomes are ever adopted into practice and may take up to 20 years to do so. In the USA, it has been estimated that 80% of the funding to medical research fails to impact on public health improvements.<sup>10</sup> It is recognised that context and external validity are important components when considering of adoption of

new trial evidence into practice. Hence the development of implementation science defined as the systematic study of how to design and evaluate a set of activities to facilitate successful uptake of an evidence-based effective health intervention into routine clinical practice.<sup>11</sup> Early inclusion of implementation scientists into clinical trial design may ensure that trials are not developed and funded without an objective assessment of the likelihood of uptake should it be successful. However, there is a tension here between enthusiastic researchers who will have dedicated many years (and many rounds of funding) to develop an exciting new concept based on sound science and implementation science focusing on the probability of utility and uptake in the context of modern healthcare. It will be of interest to see how this plays out as implementation science gains momentum and influence and whether it can translate into better clinical care and outcomes based on high-quality evidence without stifling academic science which often has limited focus on the end game in healthcare.

Sir Michael Peckham, Professor in Radiotherapy and Oncology at the Royal Marsden Hospital and subsequently the first nation director of Research and Development in the UK wrote ‘a prime objective is to base decision-making at all levels in the health service—clinical decisions, managerial decisions and the formulation of health policy—on reliable information based on research.’<sup>12</sup> We may now have the tools to take this ideal forward incorporating implementation science in our modern clinical trial design paradigms.

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