34 low-income countries and in 21 of 47 lower-middle-income countries. Finally, research programmes investigating potential cancer determinants, especially in the areas with the least described cancer burden and highest prevalence of infections, would enable validation of the estimates developed by Ward and colleagues,[2] and possibly suggest solutions to childhood cancer management in these populations.[8]

Eva Steliarova-Foucher
Section of Cancer Surveillance, International Agency for Research on Cancer, WHO, Lyon CEDEX 08, France
steliarova@iarc.fr

I declare no competing interests. The author is a staff member of WHO. The author alone is responsible for the views expressed in this Comment and they do not necessarily represent the decisions, policy, or views of WHO.

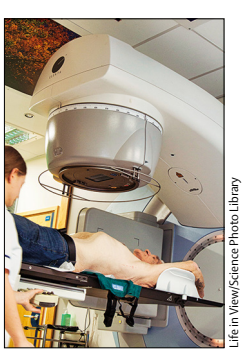
1 Steliarova-Foucher E, Colombet M, Ries LAG, et al. International incidence of childhood cancer, volume 3. 2017. Lyon, France: International Agency for Research on Cancer. http://iicc.iarc.fr/results/ (accessed Dec 20, 2018).
2 Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. *Lancet Oncol* 2019; published online Feb 26. http://dx.doi.org/10.1016/S1470-2045(18)30909-4.
3 Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer. 2018. https://gco.iarc.fr/today (accessed Dec 20, 2018).
4 Magrath I, Steliarova-Foucher E, Epelman S, et al. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 2013; **14:** e104–16.
5 Kruk ME, Gage AD, Joseph NT, Danaei G, Garcia-Saiso S, Salomon JA. Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries. *Lancet* 2018; **392:** 2203–12.
6 Kruger M, Hendricks M, Davidson A, et al. Childhood cancer in Africa. *Pediatr Blood Cancer* 2014; **61:** 587–92.
7 Boerma T, Victora C, Abouzahr C. Monitoring country progress and achievements by making global predictions: is the tail wagging the dog? *Lancet* 2018; **392:** 607–09.
8 Barr AL, Young EH, Smeeth L, et al. The need for an integrated approach for chronic disease research and care in Africa. *Glob Health Epidemiol Genom* 2016; **1:** e19.

CHISELing a path forward in the treatment of early-stage non-small-cell lung cancer

Rapid technological changes inherently conflict with the slow pace of evidence-based medicine. In technology-driven specialties such as radiation oncology, it is difficult for randomised data to keep up as treatment tools evolve. Often, new approaches are introduced into clinical practice without supporting level 1 evidence. Adoption of a useful technology into clinical practice without level 1 evidence from randomised controlled trials allows immediate access for patients, and if the technology proves beneficial, outcomes are improved. But premature adoption of a technology that is later proven to be unhelpful leads to unnecessary cost and possibly harm. Differentiating between these two scenarios in advance, before randomised controlled trials, is often impossible. Moreover, even when randomised controlled trials are launched, a large proportion of them fail, leaving us without a high level of evidence despite enormous efforts.[1] Even successful trials can be irrelevant if a technology has drastically improved since the trial was launched.

One example of this conflict is the widespread adoption of proton therapy (an expensive technology that might better spare healthy tissues than conventional photon treatment) without level 1 evidence of benefit. Only now, decades after its introduction, are large randomised controlled trials underway. With one study already reporting negative results,[2] albeit using an older technology, the results of the forthcoming randomised trials are far from certain. Nonetheless, in some centres, proton therapy is aggressively marketed, their websites promoting incorrect claims that are not supported by data.[3] We should be mindful that medical reversal—the abandonment of a treatment previously presumed to be beneficial—is common in medicine.[4] Until randomised controlled trials are done, establishing whether a new technology represents a true step forward, or a step in the wrong direction, is difficult.

In the context of these difficulties, the completed phase 3 CHISEL trial by David Ball and colleagues reported in *The Lancet Oncology*[5] is a major step forward. CHISEL tested the effect of stereotactic ablative radiotherapy (SABR) in early-stage non-small-cell lung cancer (NSCLC) and compared the therapy with older radiotherapy techniques. CHISEL enrolled patients with peripherally located stage 1 NSCLC who were either unfit for surgery or refused surgery, and randomly assigned them to either conventional radiotherapy (66 Gy in 33 fractions of 2 Gy or 50 Gy in 20 fractions of 2·5 Gy) or SABR (54 Gy in three 18 Gy fractions or 48 Gy in four 12 Gy fractions). SABR achieved improvements


Life in View/Science Photo Library

Published Online
February 12, 2019
http://dx.doi.org/10.1016/S1470-2045(18)30953-7

See Articles page 494

in freedom from local failure, the primary endpoint (hazard ratio for SABR *vs* standard radiotherapy 0·32 [95% CI 0·13–0·77], p=0·008), and overall survival, a secondary endpoint, with 2-year overall survival of 77% (95% CI 67–88) in the SABR group and 59% (44–78) in the standard radiotherapy group. SABR was well tolerated and was not associated with a decline in quality of life.

Like all trials, CHISEL has some limitations. The primary endpoint, local failure, can be difficult to ascertain on imaging in the setting of post-SABR fibrotic changes around the target.[6] This limitation is mitigated by the strong overall survival benefit detected in the trial—an endpoint unaffected by the limitations of imaging. One of the allowable doses in the standard group, 50 Gy in 20 fractions, would be considered low by today's standards, but was a common approach in some non-SABR centres when the trial was designed.

However, many unanswered questions remain. The minimum technological requirements for delivering SABR are not well established. Minimum benchmarks would be useful for centres implementing SABR, especially in developing countries. These benchmarks would include a method of accurate targeting (a planning CT scan with either motion assessment and management or immobilisation), three-dimensional conformal planning, and a method of image guidance. The optimal SABR dose and fractionation remain unknown. The risks of SABR depend on the location of the tumour; tumours adjacent to mediastinal structures require lower doses to avoid injury, but lower doses risk compromising tumour control. Ongoing studies are addressing this balance.[7]

Perhaps the most tantalising unknown is the combination of SABR with immunotherapy. Tumour cell death induced by SABR can trigger innate immunity, increase recruitment of immune cells, and activate the body's adaptive immunity.[8] Perhaps the immune-stimulatory effects of SABR in conjunction with immunotherapy will bring advances in the treatment of early-stage NSCLC; this combined treatment will be tested in upcoming randomised controlled trials.

What can we learn from CHISEL? The trial establishes SABR as the standard radiotherapy approach in patients with stage 1 NSCLC who are not undergoing surgery. A previous randomised controlled trial of SABR in early NSCLC did not show a benefit of SABR, but had several important limitations, including the fact that histological confirmation of malignancy and PET staging were optional.[9] CHISEL also teaches us that excellent 2 year overall survival can be achieved in patients unfit for surgery. Concluding that overall survival would be higher in a fitter population of medically operable patients, in which the risk of death from comorbidity would be lower, is reasonable. This idea leads to the question of whether SABR should be an alternative to surgical resection in patients who are operable. Pooled data from two incomplete randomised controlled trials,[10] published in *The Lancet Oncology*, suggested that SABR might be more effective and be associated with fewer adverse events than surgery, but firm conclusions await larger trials.

Perhaps the most important lesson from CHISEL is that the benefits of new technologies can indeed be proven in randomised controlled trials. As a speciality, we need to maintain equipoise about new interventions and enrol patients in clinical trials. We should recognise that although we ourselves might believe that our new technologies are beneficial, if we do not complete randomised controlled trials, other important stakeholders might not believe in these benefits. Colleagues might not refer patients for the new treatment and payers might not fund it. The best way for us to advance our speciality is to complete more trials such as CHISEL.

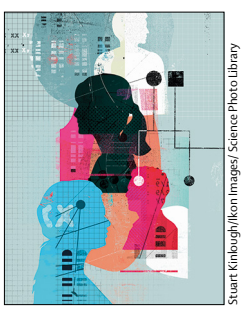
*Faiez AlShafa, *David Palma*
Division of Radiation Oncology, London Health Sciences Centre, London, ON N6A4L6, Canada
david.palma@lhsc.on.ca

We declare no competing interests.

1 Nguyen TK, Nguyen EK, Warner A, Louie AV, Palma DA. Failed randomized clinical trials in radiation oncology: what can we learn? *Int J Radiat Oncol Biol Phys* 2018; **101:** 1018–24.
2 Liao Z, Lee J, Komaki R, et al. Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer. *J Clin Oncol* 2016; **34:** 1813–22.
3 Corkum MT, Liu W, Palma DA, et al. Online advertising and marketing claims by providers of proton beam therapy: are they guideline-based? *Radiat Oncol* 2018; **13:** 43.
4 Prasad V, Gall V, Cifu A. The frequency of medical reversal. *Arch Int Med* 2011; **171:** 1675–76.
5 Ball D, Mai GT, Vinod D, et al. Stereotactic ablative body radiotherapy versus standard radiotherapy in inoperable stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a multicentre, phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2019; published online Feb 12. http://dx.doi.org/10.1016/S1470-2045(18)30896-9.
6 Nguyen T, Senan S, Bradley JD, et al. Optimal imaging follow-up schedules after stereotactic ablative radiotherapy for early non-small-cell lung cancer: findings of an international delphi consensus study. *Int J Radiat Oncol Biol Phys* 2017; **99** (suppl 2)**:** S241–42.

7 Giuliani M, Mathew AS, Bahig H, et al. SUNSET: stereotactic radiation for ultracentral non-small-cell lung cancer-a safety and efficacy trial. *Clin Lung Cancer* 2018; **19:** e529–32.
8 Popp I, Grosu AL, Niedermann G, Duda DG. Immune modulation by hypofractionated stereotactic radiation therapy: therapeutic implications. *Radiother Oncol* 2016; **120:** 185–94.
9 Nyman J, Hallqvist A, Lund JA, et al. OC-0565: SPACE—a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* 2016; **121:** 1–8.
10 Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16:** 630–37.

Assessment of breast cancer risk: which tools to use?



Stuart Kinlough/Ikon Images/ Science Photo Library

Published **Online** February 21, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30071-3

See **Articles** page 504

Risk-assessment tools are used in routine clinical practice to identify women at increased risk of breast cancer and to inform counselling about lifestyle changes, genetic testing, screening timing or modality, and eligibility for risk-reducing drugs or surgery. In *The Lancet Oncology*, Mary Beth Terry and colleagues[1] report a comparative validation of four models—the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model (BOADICEA), BRCAPRO, the Breast Cancer Risk Assessment Tool (BCRAT), and the International Breast Cancer Intervention Study model (IBIS)—used in clinical practice to provide absolute risk estimates for breast cancer on the basis of different sets of factors. Their work is an important contribution to the field in view of the need for robust, comparative assessments of risk models. Terry and colleagues assessed model calibration with data from a combination of family-based cohorts in Australia, Canada, and the USA—the Breast Cancer Prospective Family Study Cohort. In this study population, BOADICEA and IBIS were the best-performing models in terms of calibration and risk discrimination. Although the study population was large (15 732 women without breast cancer at baseline, 619 of whom developed invasive breast cancer within 10 years of follow-up), important subgroup analyses by country or by age and mutation status were limited by size. 5-year and 10-year risk estimates were well calibrated overall, but both models overpredicted risk in women in the highest risk quantile for breast cancer. This overprediction was small (eg, the predicted *vs* observed 10-year risk of breast cancer in *BRCA*-negative women was 7·1% *vs* 6·1% for BOADICEA and 7·5% *vs* 6·5% for IBIS). However, the highest risk quantile included both moderate-risk and high-risk women (ie, women with a 10-year risk ≥5% or a 5-year risk ≥2·5%), and thus might not fully reflect prediction accuracy in women at high risk of breast cancer. It is also important to assess model performance in several independent study populations because both model calibration and risk discrimination are population dependent. Consistent with findings in the Breast Cancer Prospective Family Study Cohort,[1] two other reports[2,3] based on large prospective cohorts in the USA and the UK have shown overprediction of breast cancer risk in women at high risk, showing that further model improvements are needed. These studies mostly included non-Hispanic white women, similar to the make-up of the Breast Cancer Prospective Family Study Cohort. Other racial and ethnic groups have been traditionally understudied, but efforts by different groups are underway to address this important research gap.

Simpler models, such as BCRAT, are sometimes preferred over complex models because they are easier and faster to use. However, the consequence of this simplicity is lower risk discrimination at the population level and less accurate risk scores for individual women. Although differences in measures of risk discrimination, such as the concordance statistic used by Terry and colleagues,[1] might be small, more comprehensive information about risk factors could substantially improve the ability to identify women at high or low extremes of risk. For instance, a personal history of atypical hyperplasia, lobular carcinoma in situ, or high mammographic breast density can place women in the high-risk category, but these risk factors were not assessed by Terry and colleagues because of data limitations. Polygenic risk scores, which are derived from genetic testing of many common genetic variants, are a new, important risk factor for breast cancer. Although the variants are associated with small risks individually, when aggregated as a polygenic risk score, they can identify women with or without a family history of breast cancer at substantially different levels of risk.[2,4-6] Both IBIS and BOACIDEA have been extended to include information on polygenic risk (although this information was not included in the versions analysed by Terry and colleagues),[5,7] and clinical tests to measure