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Fabrikant Award Lecture

Jacob I. Fabrikant Award lecture†

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Mr. President, friends and colleagues, it is with great pleasure and humility that I accept the Fabrikant award. I am truly honoured.

We must remember that we're all 'standing on the shoulders of giants'(1). I was lucky enough to work with two of the pioneers of radiosurgery, Christer Lindquist and David Forster, both of whom worked with Leksell and inspired me to ask questions and seek the truth; or, to use scientific terminology, to seek a model that more closely emulates the truth. If you look at the previous Fabrikant award winners you will see many great names and I think we can all agree that radiosurgery would not be where it is today without the huge contribution from these giants. Our job is to build on their great work and move our discipline forward.

My SRS career kicked off on a very cold March in 1998 when I visited Stockholm to learn about radiosurgery. I was a radiotherapy physicist; I liked Linacs and fractionation and here I was being taught about single fraction treatments delivered with cobalt sources. I was not sure I wanted to be involved with this sort of treatment. The two-week course was held at the Elekta headquarters and at the Karolinska Institute. It was during this time that I realised that my hospital, the Cromwell Hospital in London, had recruited Christer Lindquist, then the director of radiosurgery at the Karolinska. Everything changed. Christer taught me, inspired me and supported me in my career and I have no doubt that I would not be here today without his nurturing care.

Once I returned to London my key job was treatment planning. I started asking a number of questions: Firstly, what is conformity/conformality? Secondly, if a gradient is important why can't we quantify it? And, thirdly, how can we compare clinical data when treatment quality appears to differ so dramatically from centre to centre? I noticed that treatment planners would often describe their plans as conformal when to me they looked nothing like it. Beauty truly is in the eye of the beholder but that's not a sound way of quantifying the quality of treatment. There needed to be a way to objectively define conformity. At that time the only tool we had was Shaw's conformity index from the RTOG Radiosurgery Guidelines (2). This simple index was great if 100% of the target was covered by the prescription isodose but if the target had subtotal coverage the index wasn't able to account for this deficiency in the treatment plan.

In 2000, I attended the Leksell Gamma Knife Society (LGKS) meeting at Squaw Valley, Lake Tahoe. As a very junior physicist in SRS, I nervously gave a talk on a *Simple scoring ratio to index the conformity of radiosurgery treatment plans*. This index, while simple, took into account the under coverage of the target as well as dose spillage into normal tissue. To my amazement, once I'd returned home, I received a letter from Danny

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Leksell who encouraged me to write a manuscript and submit this work for publication. To my further surprise the manuscript was accepted and published in the *Journal of Neurosurgery* (JNS) (3). What many people don't know is that the index published in the JNS is actually the inverse of the original index that I presented at the LGKS meeting. In my original presentation, the index varied between one and infinity while in the manuscript the index was the inverse and varied between zero (a bad plan) and unity (a perfect plan). The group from UCSF used my original index for an important clinical study which demonstrated that it was a predictor for complications (4). Even though they cited my publication, they used the original equation and described it as the new conformity index or nCI. This was quickly adopted by Accuray in their planning system and later by Zap-X.

Early on I was lucky enough to work as a consultant for Elekta and this included teaching at 'start-ups' which is the first clinical week of a Gamma Knife programme. In March 2005, I attended one of these start-ups in Catania, Sicily, with Bodo Lippitz, then the Director of the Gamma Knife department at the Karolinska. During our week together I shared my frustration about not being able to quantify gradient and particularly not being able to demonstrate to treatment planners the degradation of gradient that occurred when placing isocentres on the edge of, or even outside the target. A spontaneous brainstorming session devised an index initially called the 25%/50% ratio which I presented at the LGKS meeting in Seoul in 2006. Immediately after my talk Josef Novotny found me and suggested I was onto something. He very modestly and humbly suggested that I look at a paper that he had published with his group in Prague which demonstrated that a related index was a predictor for complications following vestibular schwannoma radiosurgery (5). This encouraged me to publish. While writing the manuscript for the index, I found, to my horror, that the Gradient Index wasn't steepest at the 50% isodose for Gamma Knife treatment plans and that often a steeper dose fall-off could be obtained by prescribing to lower isodose, typically the 40% (6). This simple Gradient Index was adopted by a number of Linac and Cyberknife centres that found that they too could obtain a steeper dose fall off by normalising their plans to a lower isodose (7,8,9).

Another index that I think may have great value in the future is the Efficiency Index (10). Efficiency is classically defined as the useful energy delivering an effect divided by the total energy required to achieve it. The index basically measures the energy deposited within the target divided by the total energy delivered within the half prescription isodose volume. If you look at the two plans (Figure 1) you can see that while the plan on the right has a better conformity, the plan on the left has a higher Efficiency Index due to its lower prescription isodose (yielding a hotter centre) and steeper dose gradient. As we heard from Dr. Dade Lunsford during his Leksell lecture this week, conformity might not be the most important parameter in evaluating the potential efficacy of a treatment plan.

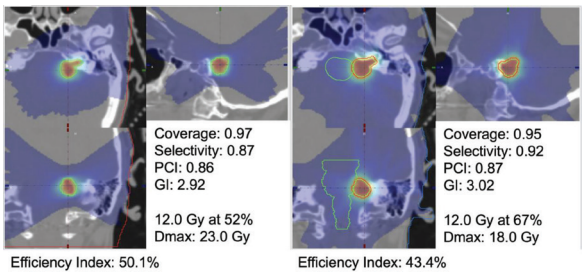

Figure 1. Two competing SRS plans with varying quality indices.

It is essential that we understand and are able to control variables that affect our treatments. Helena Sandström, in her PhD thesis, demonstrated the huge variation in target delineation amongst different radiosurgery centres (11). We need to do better in this area and all clinicians that contour need to be aware of key variables that can affect the visible extent of the tumour.

Windowing is a basic but fundamental parameter that needs to be understood by anyone involved in delineation. If a window is set where there is saturation in the tumour (eg. contrast enhanced T1 MRI) or in the bone (eg. CT) then the partial volume effect will alter the apparent volume of the target and hence the contour drawn. By widening the window and reducing saturation you will lessen the partial volume effect and get a much better agreement between your multi-modality imaging.

Another factor that can affect target delineation is the time delay between contrast injection and scanning. Kushnirsky (12) demonstrated that a 15-min delay between injection and scanning increased the conspicuity of small metastases. However, it can also increase the volume of metastases as gadolinium begins to leech out of the lesion.

I've been lucky to have had many collaborations over the years and when Caroline Chung invited me to contribute to a paper looking at the impact of slice thickness on metastasis contouring I was very grateful. This study demonstrated that slice thickness will affect not only the number of targets detected but also their volume (13). The type of contrast agent can also affect the apparent volume of the target. For the imaging of metastases, I have a personal preference for Gadavist (Gadbuterol, Bayer AG, Germany), which has a shorter T1 relaxation and not only increases the number of lesions seen but can also increase the confidence in delineation (14).

The definition of target coverage is critical but often neurosurgeons and oncologists have different approaches. I feel that there is a tendency for neurosurgeons to accept subtotal coverage of benign disease; as they assure me that benign disease doesn't always need total removal in order to gain local control. The oncologists on the other hand often believe that every tumour cell needs to receive the prescription dose (the target cell hypothesis) and so aim for 100% coverage; but they also consider adding a 'safety margin' which in my opinion is a contradiction in terms due to the significant increase in normal tissue irradiated. In a simple example (Figure 2) we have a small metastasis being covered by an 8 mm collimator isocentre. On the left we have 90% coverage then moving to the right 95% coverage then 100% coverage and finally at the far right we have coverage with a 1 mm margin. Even though each of these treatment plans would be described in the same way (i.e. prescription dose = 24 Gy), there is a 48% difference in dose delivered between the far left and far right plan to every voxel in the target and the normal tissue.

We must be mindful that in radiosurgery we have a high dose gradient both outside and inside the target and so by adding a margin we are effectively increasing the dose to not only the target but normal tissue as well. It is therefore not surprising that we tend to see an increase in complications when margins are added (15,16).

I have also been lucky enough to work with the Oxford radiosurgery group (John Hopewell, Bill Millar and Bleddyn Jones). This group has studied the effect that sublethal repair has during prolonged treatment (greater than 10 min) in reducing the biological effective dose (BED) delivered. In a cell survival assay study we were able to demonstrate the substantial increase in dose required to deliver the same amount of cell kill for prolonged irradiation times (17). For V79 cells 23 Gy, given acutely, yields a surviving fraction of 0.001%. If the exposure time is increased to 2 hours the dose required for the same amount of cell kill raises to 32 Gy. That's a 39% increase in dose required for the same effect just because the treatment time is extended.

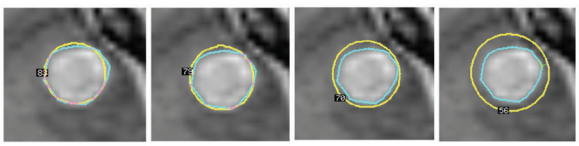

Figure 2. Four Gamma Knife treatment plans, of different coverage/normalisation for a small metastasis treated with a single 8 mm collimator to 24 Gy. Plan d) has a 48% higher dose compared with plan a) to all points in the plan.

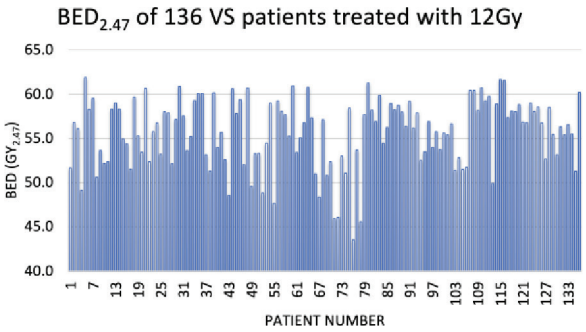

Figure 3. Variation of the Biological Effective Dose for a series of 136 patients treated for vestibular schwannoma with the Gamma Knife Model B (patients 1 to 79) and Perfexion (patients 80 to 136).

In 2018, Jones and Hopewell, in an effort to encourage clinical centres to use the BED, published a series of methods to estimate the BED of treatment plans delivered over prolonged periods (18). This allows researchers to easily estimate the BED of treatments if they have the prescription dose and overall treatment time. Applying this to clinical data (Figure 3) you can see the huge variation in BED delivered despite the fact that all treatments have the same prescription dose of 12 Gy. It should be noted that this method used the mono-exponential equation in table 1 of the paper, which is only valid for estimating the BED for treatment times of between 20 and 110 min.

We can see from the above examples there is substantial variation in BED between our intended and our delivered treatments. If we look at the variation of target definition a conservative estimate of this effect on the dose delivered is 25%. The variation of our definition of prescription dose might yield another 25%. Depending on our dose calculation algorithm used we can have another 11% variation. The BED can easily vary by 28%. If we sum these variables in quadrature we get a value of 46%. These variations are just for the Gamma Knife. If we take into account variation between other treatment platforms the difference will be even greater. It's essential that we work towards understanding and minimising the variations I have outlined so we can increase the consistency of treatments.

I spoke yesterday in my *Radiobiology for dummies* lecture about how important it is for us to understand the sigmoid curve in radiation therapy. Dose is plotted on the x-axis and the clinical effect on the y-axis. We typically have two curves, one describing tumour control and another describing complications. We want to maximise our local control while minimising complications. The difference between vertical points on the two curves, for a given dose delivered, is called the therapeutic window or ratio. When we ignore the variables I

have outlined and plot data for a clinical cohort, the sigmoid curves flatten and result in a reduced therapeutic window. It is therefore critical for our patients and for our own research that we account for, and try to reduce, these variables in our treatments.

We have advanced tremendously in our understanding of SRS but I feel that there are a number of actions that we need to take to improve our current level of research. In particular we need to understand and, more appropriately, apply statistics to our work.

Firstly, we need to understand confounding variables. The key confounding variable in SRS, when looking at dose and complications, is target volume. We know that volume is critical and that larger volumes lead to a greater incidence of complications. For intracranial SRS we treat targets that may be between 0.002cc and 20cc. This variation is a factor of 10,000. One study, in an attempt to avoid volume effects, divided volumes between those less than and greater than 5cc. Although this is technically multivariate analysis it will not eliminate volume effects. Finer divisions of the range are required. If you wanted to divide targets into bins of a 10% volume range you would need 97 bins to accommodate the full range of target volumes. Clearly we need 'big data' in order to eliminate volume as a confounding factor – perhaps tens of thousands of treatments. Studies that have claimed, for example, that a high conformity is a predictor for radionecrosis (19, 20) or that Gradient Indices of greater than three reduce complications in meningioma radiosurgery (21) have not dealt with volume as a confounding factor adequately. The conclusions of these studies, which effectively suggest that decreasing the amount of normal tissue irradiated increases the toxicity to that tissue needs some convincing evidence as it completely goes against our understanding of radiobiology. Therefore, we need to look for confounders and bias before publishing.

Secondly, there is a tendency in the literature for 'data dredging' or 'p-value trawling'. What does the p value mean? If you search for a $p<0.05$ event in random data you would expect to find one $p<0.05$ event in every 20 relationships you explore. That's quite a high probability, especially if you are looking at multiple relationships. It is essential to create a hypothesis in advance of statistical analysis or you will simply detect and publish naturally occurring chaos (22).

Thirdly, there appears to be an underlying consensus that a value of <0.05 is required in a study in order for it to be worthy of publication. This encourages an excessive number of relationships to be explored within the data in order to find a 'significant' value. Junior members of departments, who often have the least scientific training, are often burdened with research and there is a tendency to use statistics software as a 'black box'. Well conducted studies with no significant findings should still be published. Reviewers and journal editors are at fault here.

Fourth, garbage in equals garbage out. It is critical that we perform error checks on our clinical data in order to improve the quality of the input into our studies. This is particularly the case if we're looking at effects at the bottom or top of the sigmoid curve where achieving adequately powered statistics are difficult. I've been involved in looking at clinical data for trigeminal neuralgia treatments from a number of centres. I always create a simple error check by ensuring a parameter, equivalent to the prescription dose divided by the product of beam on time, reference dose rate and the proportion of active sectors, remains an approximate constant. I have used this technique to identify parameters that are incorrect. The error rate is typically between 1 and 5%. It's also important that we understand, particularly for functional treatments, that the output factor for the 4 mm collimator on the Gamma Knife changed by 9% in 1998. All Gamma Knife treatments prior to this date need a 9% adjustment in the prescription dose. This means that, for example, 90 Gy pre-1998 is actually 97.9 Gy. There are a number of trigeminal neuralgia studies whose conclusions should perhaps be questioned because the actual dose delivered has not been correctly recorded in that study.

Fifth, we must be aware of study bias. Can we really compare two different treatment platforms if patients are treated at different hospitals by different clinical teams, who are imaging and expressing complications in potentially different ways? (23) We must also be also be aware of the phenomenon known as Simpson's paradox. This fascinating effect can lead to incorrect conclusions being drawn because of the weighting of data within the study.

We have come a long way but the evolution of SRS is continuously held back by dogma; tenets of the SRS/radiation therapy faith that blind us to asking questions. Identifying and rejecting dogma may be more valuable than producing fresh research. Below is a list of ideas that may need to be put aside if we are to move forward:

1. *'Physical doses are biologically equivalent'.* Thanks to the work by Hopewell and Millar we now know that the biological effect of treatments with different delivery times are not the same.(18) Furthermore, each treatment has a distribution of BED that is different from the physical dose distribution. In our work looking at the role of the concept of BED in treatment planning in radiosurgery (24) we were able to show that for vestibular schwannomas indenting the brainstem, even a 14 Gy treatment with the Gamma Knife (max 85 $Gy_{2.47}$) had a peripheral BED that was

lower than the widely accepted tolerance dose for the entire brainstem (25×2 Gy, 90.5 $Gy_{2.47}$). This is backed up by the almost complete absence of brain stem toxicity from Gamma Knife SRS in the treatment, or even retreatment of vestibular schwannoma (25).

2. *'Cell survival studies and animal models don't translate to clinical data'*. We must remember that all damage, and the vascular, immunological effects that are a consequence of the original damage, is mediated by DNA injury and is therefore subject to sub-lethal repair effects. Cell survival studies(18), animal models (24, 26), DNA strand break studies (27) and now clinical studies (28, 29, 30) are all compatible with the bi-exponential repair model championed by Hopewell et al (24).
3. *'Vascular effects harnessed by SRS are 'different' compared with conventional radiation therapy'*. However, vascular effects are also common in radiation therapy despite the much lower BED being delivered. There's no evidence that vascular effects wouldn't be as common in conventionally fractionated treatments if a similar BED was delivered. With the accommodation of sub-lethal repair effects (ignored during the period of the 1990's and 2000's when the applicability of the LQ model for SRS was being questioned) the LQ model may be equally valid for SRS treatments.
4. *'Fast growing tumours (or even all tumours) have an alpha beta ratio of 10.'* We must revisit the radiobiology literature from almost 50 years ago to find the source of this 'tenet of faith'. In 1976 Douglas and Fowler reported a study on the fractionation of mouse skin (31, 32). Schedules varied between 1 and 64 fractions delivered over a period of 8 days. This meant that some fractions were delivered as little as 3 hours apart. The incomplete repair between these short gaps was a fundamental flaw in this study but at the time Fowler believed, incorrectly, that repair was faster when smaller dose fractions were given. This effectively increased the apparent alpha beta ratio in the study. Consequently, a fractional equivalent (FE) plot was made and an alpha beta of 10.4 was derived. The second fatal flaw in this study was to postulate that because the epithelial layer of the skin has a rapid cell turnover, and fast-growing tumours have a rapid turnover, then tumours might also have an alpha beta ratio of 10. These two incorrect assumptions led to the derivation of the alpha beta ratio which is recited repeatedly; each time harming our understanding of radiosurgery and radiotherapy. It is also one of the reasons that SRS had so many critics in the early years. The fact that SRS is so successful in treating its mainstream indications is proof enough that the alpha beta ratios of these targets are much closer to normal tissue, and even some are likely to be lower (33).
5. *'The brainstem and optic apparatus are serial organs'*. Both these organs at risk (OARs) are subject to the radiobiological laws of dose and volume. I question why a clinician should worry about point doses of 12 Gy to the brainstem when treating a vestibular schwannoma but accept a 35 Gy point dose to the brainstem for the treatment of trigeminal neuralgia (34). This demonstrates discrepancies in clinical practice and radiobiological thinking. Maximum point doses to OARs are a blunt tool and we have an opportunity to do much better. Animal studies have shown that dose and volume are both critical ingredients for the precipitation of radionecrosis (35). Spinal tolerance doses in radiation therapy teach us that the length irradiated has a significant effect on the tolerance dose (36). Similarly, functional studies looking at the variations in dose volumes for gamma capsulotomy for OCD have suggested that by fixing the dose-volumes a greater reproducibility of treatment can be achieved (37, 38).

   We have a great opportunity to improve our quality of research but we cannot use doses published by other groups unless we understand their definition of target and dose. Subtleties between apparently similar treatments are often overlooked. Reporting planning indices and the BED may help us to quantify treatments and, importantly, empirically derive better treatments.

   We must strive to improve the quality of our research and continue to question some of the key tenets of SRS which are holding us back and may turn out to be unsubstantiated dogma.

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