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Reports of unexpected late side-effects of accelerated partial breast irradiation – radiobiological considerations

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Keywords

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Three reports[1–3] in the Journal on late side-effects after accelerated partial breast irradiation (APBI) stimulate valuable debate about the safety of the treatments delivered. All use the same hypofractionated schedule, 3.85 Gy x 10 fractions delivered twice daily with a minimum 6-hour inter-fraction interval on 5 consecutive days. Interest is sharpened because this is the exact schedule used in the ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 phase III trial with a target sample size of 4,300 patients of whom more than 3,000 are already accrued. In one report, Chen et al.[1] analyze 4-year data on cosmesis and toxicity in 94 patients treated with 3D conformal radiotherapy (3D-CRT). They conclude reassuringly that the outcomes of this treatment "…*appear comparable to other experiences with similar follow-up*". The two other reports raise warning flags. Hepel and colleagues[2] from Tufts Medical Center and Brown University document late side-effects in 60 patients treated with 3D-CRT and conclude that this schedule results in "…*remarkably high moderate-to-severe late normal tissue effects*". Similarly, Jagsi et al.[3] from University of Michigan analyze the cosmetic outcomes in 34 patients treated with IMRT and conclude that the "…*hypofractionated schedule and parameters used [in NSABP B-39/RTOG 0413] …may be suboptimal*". All three are well-conducted studies from highly respected groups of experienced investigators and the conclusions of all three have to be examined closely. From a radiation biology perspective, factors to be considered include the fractionation sensitivity of late reacting normal tissues, recovery between fractions delivered on the same day and the volume effect. Recovery has traditionally been referred to as Repair, but the former term is preferred here as other processes than cellular repair may be involved.

Starting with fractionation sensitivity, how do these reports fit with recent data from large randomized controlled trials[4–8] testing the safety of hypofractionation for whole breast

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irradiation (WBI) when total dose is adjusted according to the linear-quadratic (LQ) bioeffect model? Applying the LQ model with α/β=3.4 Gy, the current estimate for changes in breast appearance from the WBI hypofractionation trials[4], suggests that 38.5 Gy in 10 fractions is equivalent to 52 Gy in 2-Gy fractions. This equivalent dose is just not high enough to explain higher than expected adverse effects of APBI in 2 out of 3 reports. The more important influence of the 6-hour interval between daily fractions will have to be evaluated.

The first indications that inter-fraction recovery kinetics were slower for human endpoints than those estimated from experimental rodent models came from analyses of the impact of inter-fraction interval on the incidence of mucositis in two RTOG head and neck BID trials: RTOG 7913 published by Marcial et al.[9] in 1985 and RTOG 8313 published by Cox et al.[10] in 1991. More evidence, and the first crude numerical estimates of recovery half times, $T_{½}$, of 3 to 4 hours for oral mucosa[11], came in 1996. For recovery half times as long as these, recovery cannot be assumed to be complete in the overnight interval between the last fraction in one day and the first fraction the following day. A generalization of the LQ-model that can take this phenomenon into account has been developed[11, 12] and this model is used in the following. For late skin telangiectasia after postoperative radiotherapy for breast cancer, Ingela Turesson performed a series of elegant experiments treating left- and right-side internal mammary chain fields twice or once a day in the same individual, demonstrating that recovery was not complete after 4-hour, or even 8-hour, intervals[13] (published in 1988 and 1995, respectively)[14]. In a 1989 paper, Turesson and Thames estimated $T_{½}$ for skin telangiectasia at 3.4 to 3.6 hours[15] but the model was complicated by the inclusion of an overall time factor and the authors reported that the data could also be adequately fitted using a much shorter $T_{½}$. Further quantitative estimates of recovery half times for late endpoints in humans were derived from the CHART (Continuous Hyperfractionated Accelerated Radiation Therapy) head and neck trial[16]. This trial was particularly sensitive to recovery kinetics as three fractions per day were delivered with a 6-hour interval over 12 consecutive days. The recovery half-time, for telangiectasia was estimated at 3.8 hours and for fibrosis at 4.4 hours. Applying the telangiectasia $T_{½}$ estimate to Turesson's schedule of 25 twice-daily fractions of 2 Gy with an 8-hour interval produces an equivalent dose in 2 Gy fractions of 56.5 Gy, in good agreement with the ~55 Gy estimated directly from her clinical data. These data provide strong independent support for using the long recovery half-times estimated from CHART in bio-effect calculations.

The atrophic/fibrotic radiation response pathway is a major component of many late radiation side-effects and although the pathogenesis is complex[17], there is a clear dose-incidence relationship and a well characterized fractionation sensitivity of the clinical endpoints that reflect this response pathway[18]. Fibrosis is strongly associated with breast appearance and cosmesis, as illustrated by Hepel et al. who estimate an odds ratio of 16 for developing fair/poor cosmesis in patients developing grade 2–4 subcutaneous fibrosis after APBI. In the absence of recovery kinetics data for breast appearance, we base the following estimates on recovery parameters estimated for fibrosis.

Using the 4.4 hours $T_{½}$ estimate for fibrosis and α/β=3.4 Gy, the ABPI schedule is estimated to be equivalent to 64.9 Gy in 2 Gy fractions. Repeating this estimation with α/β=2.8 Gy, a pooled estimate of the α/β ratio for late changes in breast appearance from the START A & B trials, the START pilot trial and the FAST trial[19], estimates the equivalent dose at 68 Gy. The estimated equivalent doses taking incomplete recovery into account, 65 – 68 Gy, predict a very high incidence of late effects if delivered to the whole breast. For example, the incidence of moderate and severe changes in skin appearance after doses in this range would be expected to be 75–82% compared with 31% after 50 Gy in 2-Gy fractions based on the data from the START A trial[4]. The challenge is to quantify the effect of reduced volume

when applying WBI dose response data to APBI, and this is returned to later. Meanwhile, for human tumors, inter-fraction recovery kinetics data are sparse, verging on non-existing. With the current best α/β-estimate[4] for sub-clinical breast cancer being 4.6 Gy (95% CI 1.1–8.1 Gy), a hypofractionated regimen is expected to be hot on the tumor as well. If – and again there are no data to support this – recovery kinetics are similar for tumor and late normal tissue effects, the equivalent tumor dose from the NSABP/RTOG schedule would also be more than 60 Gy. There is considerable uncertainty here, both in the α/β estimate for breast cancer as well as the assumed long $T_{½}$, but under these assumptions the *efficacy* as well as *toxicity* would increase by the use of a hypofractionated twice-daily schedules compared to a single-fraction-per-day schedule. All in all, the APBI dose delivered by external beam radiotherapy appears unnecessarily high for a population of low risk patients.

What else may be influencing risk of adverse effects? Adjuvant cytotoxic chemotherapy[20] and endocrine therapy[21] have long been recognized as risk factors for radiation-induced fibrosis after postoperative radiation therapy for breast cancer and this was also confirmed in the large EORTC boost trial[22]. None of the three APBI studies seem to differ with respect to use of drugs (see Table 1). This leaves us with the dose-volume parameters as a possible explanation for the varying conclusions from the ABPI studies. Table 1 summarizes dose parameters reported in the 3 published reports supplemented by personal communication with the authors, whose additional comments have been most valuable. V_x is defined as the volume, measured in cubic centimeters, receiving more than x% of the prescribed dose. It is generally accepted that there are strict volume constraints that must be met if late adverse effects after APBI are to be minimized. However, careful examination of the dose-volume parameters for the three studies does not reveal major differences that could explain the different conclusions in the three reports. It would certainly be of great interest if the 3 groups were able to undertake and publish a combined analysis that investigates the dose-volume effects in detail. There are strong indications of a dose-volume effect in the literature. Borger et al.[23] published a retrospective analysis of tumor bed boost therapy delivered by iridium implant after 50 Gy in 25 fractions WBI. In an analysis of 404 patients, a four-fold increase in the risk of fibrosis was reported for every 100 cc increase in irradiated boost volume at a median follow up of 70 months (range 30–133). In a prospective randomized trial of APBI versus WBI, Polgar et al.[24], performed a non-randomized sub-group comparison of adverse effects of APBI delivered by interstitial brachytherapy (N=85) versus WBI with external 6–9 MV photons (N=93). This comparison excluded cases receiving PBI using electrons and patients receiving WBI on a ^{60}Co machine. The prescribed brachytherapy dose to the 100% isodose was 36.4Gy in 7 fractions of 5.2 Gy treating twice daily with a minimum 6-hour interval, and the mean V_{100} was 63 cc (range 27–120 cc). The equivalent dose in 2-Gy fractions for subcutaneous fibrosis, using the same assumptions as above, was 74 Gy. The WBI dose was 50 Gy in 25 fractions over 5 weeks prescribed to 95% of the dose to a reference point in the centre of the breast. Rates of fair or poor cosmesis scored using the Harvard criteria were 19% after APBI, despite the much higher equivalent dose in 2-Gy fractions in this group, compared to 34.4% after WBI at median follow up of 66 months (18–101 months). These data are supportive of a powerful volume effect, even though brachytherapy data are not directly comparable to APBI data generated by external beam irradiation. A further impression after brachytherapy is offered by Wazer et al.[25] in a retrospective analysis of risk factors for late normal tissue effects after APBI delivering 34 Gy in 10 fractions over 5 days, where they offer a ‘reasonable rule of thumb’ that <60% whole breast reference volume should receive ≥50% of prescribed dose, a limit applied by Chen et al.

It may also be informative to compare the findings of the three APBI reports with the effects of the tumor bed boost dose after WBI. EORTC 22881–10882, the boost versus no-boost trial by Bartelink et al.[26], randomly allocated >5,000 patients to 50 Gy in 25 fractions WBI

with or without a 16 Gy in 8 fractions boost by electrons or photons. Median V_{95} for simulation-based treatment plans were only 99 cc (range 9–628) for photons and 98 cc (13–651 cc) for electrons[27]. The boosted volume received 66 Gy in 2 Gy fractions, very close to the above estimated equivalent dose for 3.85 Gy x 10 twice daily fractions. Severe and moderate fibrosis in the EORTC trial was seen in 4.4% and 28% of the cases at 10 years, respectively. The 95% confidence intervals (CI) were very narrow as a result of the large number of cases in the trial. In comparison, the rates of moderate and severe fibrosis in the no-boost arm were only 1.6% and 13%, so most of the recorded fibrosis appears to be attributable to the applied boost, making this an interesting model for APBI. Table 1 summarizes the incidence of fibrosis in the three APBI studies – apparently in the same ballpark as the 10-year EORTC data. However, the difference in follow-up times needs to be taken into account. Estimates suggest that 90% of the ultimate incidence of fibrosis is expressed by around 4 years after radiation therapy, depending on the grade of reaction and the intensity of the schedule. At 2 years the incidence of moderate and severe fibrosis in the EORTC trial was roughly half that at 10 years[22]. As APBI data mature, rates of significant fibrosis may exceed that in the EORTC trial as a consequence of larger target volumes.

Both the ASTRO[28] and the German[29] consensus statements on APBI pointed to the lack of long-term follow-up in the majority of the ABPI reports as a concern when judging the safety of these regimens. The across-study averages of the median follow-up period for several APBI techniques were short at the time of the ASTRO consensus statement: 2.3 years for MammoSite, 2.1 years for intraoperative and 1.0 years and 0.5 years for external beam APBI with photons and protons, respectively. It would not be surprising if techniques that initially appeared to be almost without side-effects, turned out to produce some level of late effects as data mature. The median follow-up (and range) reported by Jagsi et al. (2.5 years, range: 1.5 – 3.7 years), Hepel et al. (1.3 years, range: 0.5 – 3.6 years) and Chen et al. (4.2 years, range: 1.3 – 8.3 years) provide us with valuable insights. Paradoxically, it is the two studies with comparatively short follow-up that raise concern.

Finally, it may be useful to look at the cosmesis data reported from the three APBI studies from a biostatistics point of view. Table 1 summarizes the incidence of “unacceptable”, defined as “fair” or “poor”, cosmesis in the three studies: 13% in Chen’s study, 18% and 21% in the studies by Hepel and Jagsi, respectively. A formal statistical comparison should be taken with a grain of salt, but neither the Hepel nor the Jagsi study find an incidence of unacceptable cosmesis that is statistically significantly higher at the 5% significance level than the 13% reported by Chen et al. However, the incidence in Chen’s study is based on patients who completed at least 3 years of follow-up, whereas the incidence estimates in the two other studies result in part from patients with a relatively short follow-up. On the other hand, the study by Jagsi et al. was stopped early due to the observation of 7/34 patients with “fair” or “poor” cosmesis. An element of early stopping and publication bias cannot be ruled out: the impetus to analyze and publish these data may in part have come from the fact that late effects looked worse than initially expected.

All teams deserve much credit for sharing their early experiences with the clinical community. While the level of late side-effects seen in the reports by Jagsi and Hepel seem unexpected, they are not inexplicable when the effect of incomplete recovery between fractions is taken into account. A final verdict on the long term cosmetic outcome as well as a characterization of efficacy of APBI using the NSABP/RTOG schedule will almost certainly come when mature data from the ongoing trial become available. At that point, it can be rationally considered whether once-daily delivery is preferable to the current BID delivery or whether a change of dose-fractionation is warranted. An important secondary analysis of the trial data will relate to the relative importance of various dose-volume metrics in achieving an acceptable cosmesis after this regimen. Meanwhile, it seems

premature on the current grounds to question APBI in general or the NSABP/RTOG schedule and dosimetric constraints. Review by the NSABP Data Monitoring Committee offers powerful reassurance that patients treated within the B-39 trial are experiencing low rates of adverse effects. In conclusion, the research community has underestimated the effects of incomplete recovery when using this schedule of APBI, requiring a strong dose-volume effect to protect the large majority of patients from significant adverse effects.

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Table 1

Comparison of APBI toxicity reports 2009

	Chen et al.	Hepel et al.	Jagsi et al.
No. of patients	94	60	34
Follow up, median (range)	4.2 years (1.3–8.3) years	1.3 years (0.5–3.6) years	2.5 years (1.5–3.7) years
Patients receiving cytotoxic chemotherapy	12%	5%	18%
Patients receiving endocrine therapy	55%	52%	35%
Mean (range) excision cavity volume	*25 cc (3–104)	42 cc (6–266)	40 cc (10–102)
Mean (range) partial breast PTV_EVAL	*269 cc (62–623)	296 cc (67–950)	185 cc (60–382)
Mean (range) PTV_EVAL/whole breast volume	17% (8–27)	*19% (2–43)	*15% (6–27)
Mean (range) V100/whole breast volume	24% (2–39)	*16% (3–55)	*18% (7–30)
Inter-quartile range V100/whole breast volume	-	*10–20%	*13–22%
Mean (range) V50/whole breast volume	49% (31–61)	*42% (11–58)	*38% (17–65)
Moderate or severe (grade 2+) fibrosis (95% CI)†	9% (4–16)	25% (15–38)	9% (2–24)
Severe (grade 3+) fibrosis (95% CI)†	3% (1–9)	8% (3–18)	0% (0–10)
“Poor” or “Fair” cosmesis (95% CI)†	‡13% (6–22)	18% (10–30)	21% (9–38)

Abbreviations: PTV_EVAL = planning target volume for evaluation to within 5 mm of skin and bound by lung/chest wall interface.

*Data kindly provided via personal communication with authors. Selected parameters for Jagsi et al. were recalculated using a definition of whole breast volume comparable to Hepel et al. and Chen et al.

†Estimated by us assuming binomial statistics for responders/subjects given in the papers

‡Group of 80 patients with a complete follow-up of at least 36 months