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RapidArc and Tomotherapy H&N Plans & Treatments in 2017

On July 20th Accuray issued a press release (PR) highlighting a paper-in-press by Bibault, et. al. entitled Clinical Outcomes of Several IMRT Techniques for Patients with Head and Neck Cancer: A Propensity Score-Weighted Analysis.[1] The article is critical of RapidArc® (RA) & favors Tomotherapy® (TT) treatments for H&N CA.

Their press release omits key facts and leads to erroneous conclusions in suggesting that *New Data Show Tomotherapy® System Superior to RapidArc® in Achieving Local Control of Head and Neck Cancers*. It categorizes all RapidArc plans for H&N as the same, suggesting that a patient treated today will get poorer outcomes than TT. It states: "At 18 months, the local control rate and cancer-specific survival rate were significantly better in the TomoTherapy patient group than in the RapidArc group" and that "significantly reduced doses outside the tumor, leading to better acute salivary function than with RapidArc." It does not mention that this specific patient cohort was treated 5 to 7 years ago, in the earliest days of both techniques. There are also multiple clinical issues with the paper and release which are discussed below.

Background: The paper analyzes data from 166 patients accrued during 2 years beginning in early 2010 from 14 French centers, 92 of whom were treated with RapidArc and 74 of whom were treated with Tomotherapy, in a prospective un-randomized trial ART-ORL Trial accessible at www.ClinicalTrials.gov. Based on system-site installations at the time, it was determined that 6-7 of the sites had RapidArc and 5-6 had Tomotherapy. Two sites with a third VMAT technology (SmartArc®) were not included in the analysis because of poor accrual.

What are the facts? How does one accurately interpret the press release and clinical paper? **Five Key Points**

- *The Accuray press release fails to mention that the ART-ORL Trial 's primary design goal was to do a **cost analysis study, not a clinical outcomes study**. That analysis was published in 2016[4], and concluded that RapidArc* "should be considered superior … given the current state of knowledge" *based on quality, efficiency and total system cost.*
- *The Accuray press release fails to mention confounding clinical factors that could have played a part in the trial outcomes. Patient and tumor characteristics such as HPV (human papilloma virus) status will have a much more important impact on tumor control than any treatment details.*
- *The Accuray press release only highlights salivary disorders as a disfavor in the RapidArc group. It fails to bring up cutaneous toxicities as a disfavor in the TT group, which was also detailed as a toxicity in the paper.*
- *The Accuray press release categorizes all RapidArc treatments as the same. It omits the key point that all patients treated in this study (2010-2011) were treated with the earliest versions of RapidArc compared to treatments of potentially more developed versions of Tomotherapy given the relative product release cycles.*
- *In the March 2017, 238 participants from 34 countries participated in the 2017 International Radiotherapy Plan Competition. RapidArc Eclipse users generated the highest scoring H&N plans. They showed that RA plans were equivalent to or better than those of TT participants. PRs on Varian's Website (3/29/17 & 7/18/17) point to the outcomes. Accuray knew their 30 users participated in this competition, whose results were released to the public in June 2017. They were therefore misleading by selectively omitting plan equivalence or superiority information from the July 20 press release, which is required by Fair Balance reporting requirements.*

Propensity Analysis vs Randomization: A significant point highlighted by the authors was "the main limitation of this trial was that it was not randomized" which was "not possible as participating centers offered only one of the competing arc therapy techniques." Instead, a *statistical technique* known as "propensity score analysis by inverse probability of treatment weighting (IPTW)" was used to compare the outcomes of the two techniques. The conclusion states: "These results should be explored in a randomized trial."

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Clinical Outcomes Explanation: The paper and PR attempt to make the claim that plan quality and inhomogeneity for RA are to blame for the different outcomes as compared to TT stating: "This difference could be explained by the better dosimetric homogeneity of Tomotherapy, as we showed in the dosimetric analysis of this trial (5)." The paper also states that TT "provided a more homogeneous dose distribution with an increased Non Tumoral Integral Dose (NTID)." However, the cited references[2-4] don't support this level of negative analysis. Further, this paper did not directly address planning. Finally, there are many other confounding factors that could result in these negative outcomes.

Confounding Factors: Patients characteristics such as HPV (human papilloma virus) status are not known. More HPV-negative patients in the RA group, could easily explain the differences in outcomes, for example. The authors explain tumor control, and consequently disease-free survival, by pointing to more homogeneity doses with TT, and better coverage of target areas. But, homogeneity does not necessarily explain better control. Also, target coverage is a reflection of adequate delineation and planning. Center-to-center differences in target coverage could easily explain differences in outcomes. Their hypotheses do not explain the large difference between the techniques with respect to tumor control. If anything, this points to the possibility of differences in tumor characteristics such as HPV in both groups.

Primary Purpose of the Trial was Economic: Clinical trials are designed to answer specific questions. The **primary objective** of the ART-ORL Trial was to "assess the various of costs between tomotherapy and Intensity Modulation Radiation Therapy" and to "realize a Health economic evaluation of the various cost between tomotherapy and Intensity Modulation Radiation Therapy". There were 4 secondary measures of the trial, the first two of which were also economic. Only the latter two secondary measures of the trial had to do with clinical results. The Cost Analysis of the trial was published in IJROBP 2016 by Perrier[4] which concluded: "The cost of TomoTherapy appears to be higher than that of RapidArc therapy in patients with head and neck cancer. This is due mainly to longer treatment sessions, higher price of the accelerator, and higher costs of maintenance." Most importantly it concludes, "Because the numbers of *acute adverse events* during RT were not significantly different, VMAT RapidArc, with a lower cost, should be considered superior in head and neck patients given the current state of knowledge." It seems a bit unusual that a paper based on the same trial data could come up with two different clinical conclusions within 12 months, & years after data collection.

Not all RapidArc Planning is the same: This ART-ORL Trial was initiated over 7 years ago, when RapidArc was first released. Based on the install dates of those centers, Eclipse version 8.x was used for most, if not all, of the treatments. This early release of Eclipse was reported in prior literature to produce inferior plan quality to the potentially more advanced TT planning at the time. The clinical outcomes from a 24-month study ending in February 2012, cannot be translated to outcomes using today's RapidArc planning and delivery. Newer papers using more up-to-date versions of Eclipse[6-8] show equivalent RA plan quality compared to TT. These and other papers with newer versions of RapidArc for H&N should have been referenced in the publication.

Chemotherapy Unknowns: Chemotherapy is typically used as adjuvant therapy in H&N cancer and the therapy regimen includes carboplatin or cisplatin. In this study, 29 patients were also randomized to cetuximab[5]. With 12 centers involved, small differences in chemo administration can make large differences in outcomes including local regional control, cancer specific survival, and various toxicities.

Risk Stratification Unknowns and Toxicities: Risk stratification is subjective. Center-to-center differences in stratification could account for differences in outcomes. The paper states that regarding short term toxicities "salivary disorders were significantly most frequent in RapidArc group" but does not include that "cutaneous toxicities were most frequent in TomoTherapy." There are many potential reasons for those toxicities that are not explored.

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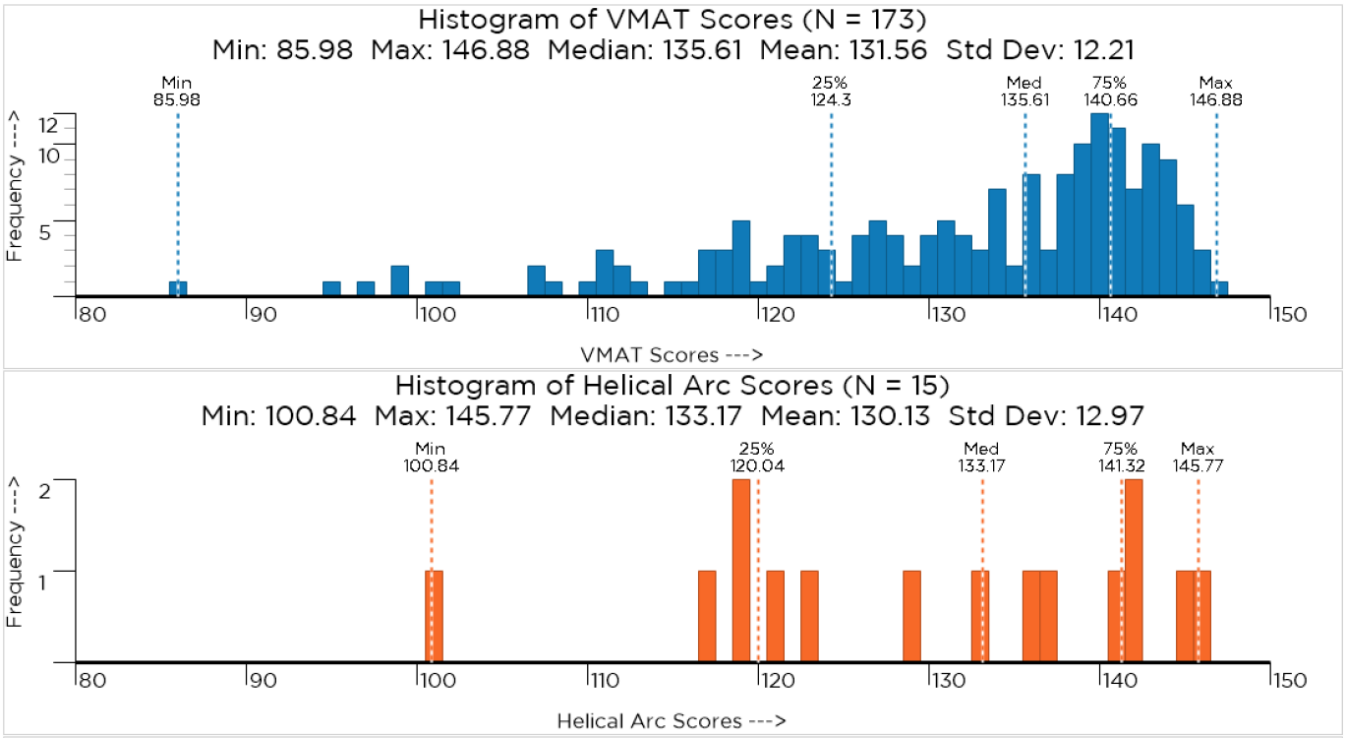
Final Comments: Two recent multicenter treatment planning competitions in the Spring of 2017 show current plan quality comparison results between these two modalities. The results of these March 2017 QADS (quality assurance and dosimetry) planning competitions, released in June 2017, showed Eclipse RA plans to be *at least equivalent* to TT Plans for H&N treatments. In fact, as shown below, Eclipse RA plans generated the highest scoring plans beating TT plans for the top spots. A PowerPoint presentation of these results is available at: https://cdn.proknowsystems.com/resources/plan-studies/instances/2016-10-QADS-TG244-HN/2017-QADS-TG244-Plan-Study.pdf

2017 QADS Head and Neck Plan Study



Again, Fair Balance dictates that these results should have been reported in the Accuray Press Release.

Other links are listed below

http://newsroom.varian.com/2017-07-18-Varian-Eclipse-Users-Generate-Highest-Scoring-Plans-in-International-Treatment-Plan-Competition (source link: http://radiationknowledge.org/)
http://newsroom.varian.com/2017-03-29-Varian-Eclipse-Customers-Achieve-Top-Scores-in-International-Treatment-Plan-Studies (source link: https://blog.proknowsystems.com/planning/2017-qads-plan-study-results-and-peer-education/)

Summary:

- ***RapidArc H&N plans are at least comparable to Tomotherapy plans in terms of plan quality.***
- ***There is no evidence to suggest that current RapidArc plans are inferior to Tomotherapy plans.***
- ***RapidArc treatments are more efficient than Tomotherapy treatments.***

For more information, please contact Varian Medical Systems.

Citations:

1) Bibault JE, Dussart S, Pommier P, Morelle M, Huguet H, Boisselier P, Coche-Dequeant B, Coche-Dequeant B, Alfonsi M, Bardet E, Rives M, Calugaru V, Chajon E, Noel G, Mecellem H, Vernat SS, Perrier L. Giraud P. Clinical Outcomes of Several IMRT Techniques for Patients With Head and Neck Cancer: A Propensity Score-Weighted Analysis. Int J Radiat Oncol Biol Phys. 2017 Jun 27. pii: S0360-3016(17)33522-8.. [Epub ahead of print]
2) Vernat SS, Ali D, Messina C, Pommier P, Dussart S, Puyraveau M, Viard R, Lacornerie T, Lisbona A, Fenoglietto P, Mazurier J, Garcia R, Hangard G, Zefkili S, Makovicka L, Giraud P. Intensity modulated arc therapy in bilaterally irradiated head and neck cancer: a comparative and prospective multicenter planning study. Cancer Invest. 2014 Jun;32(5):159-67.
3) Servagi Vernat S, Ali D, Puyraveau M, Viard R, Lisbona A, Fenoglietto P, Bedos L, Makovicka L, Giraud P. Is IMAT the ultimate evolution of conformal radiotherapy? Dosimetric comparison of helical tomotherapy and volumetric modulated arc therapy for oropharyngeal cancer in a planning study. Phys Med. 2014 May;30(3):280-5.
4) Perrier L, Morelle M, Pommier P, Boisselier P, Coche-Dequeant B, Gallocher O, Alfonsi M, Bardet E, Rives M, Calugaru V, Cost Analysis of Complex Radiation Therapy for Patients With Head and Neck Cancer. Chajon E, Noel G, Mecellem H, Pérol D, Dussart S, Giraud P., Int J Radiat Oncol Biol Phys. 2016 Jun 1;95(2):654-62.
5) Bibault JE, Morelle M, Perrier L, Pommier P, Boisselier P, Coche-Dequéant B, Gallocher O, Alfonsi M, Bardet É, Rives M, Calugaru V, Chajon E, Noël G, Mecellem H, Pérol D, Dussart S, Giraud P. Toxicity and efficacy of cetuximab associated with several modalities of IMRT for locally advanced head and neck cancer. Cancer Radiother. 2016 Jul;20(5):357-61.
6) Franzese C, Fogliata A, Clerici E, Franceschini D, Villa E, D'Agostino G, Navarria P, Mancosu P, Tomatis S, Cozzi L, Scorsetti M. Toxicity profile and early clinical outcome for advanced head and neck cancer patients treated with simultaneous integrated boost and volumetric modulated arc therapy. Radiat Oncol. 2015 Nov 6;10:224.
7) Differding S, Sterpin E, Hermand N, Vanstraelen B, Nuyts S, de Patoul N, Denis JM, Lee JA, Grégoire V. Radiation dose escalation based on FDG-PET driven dose painting by numbers in oropharyngeal squamous cell carcinoma: a dosimetric comparison between TomoTherapy-HA and RapidArc. Radiat Oncol. 2017 Mar 23;12(1):59.
8) Moncharmont C, Vallard A, Guy JB, Prades JM, Rancoule C, Magné N. Real-life efficacy of volumetric modulated arc therapy in head and neck squamous cell carcinoma. Eur Ann Otorhinolaryngol Head Neck Dis. 2017 May;134(3):165-169.

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