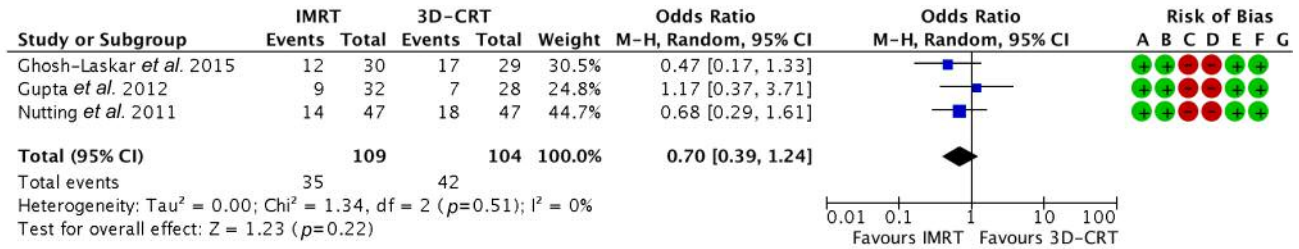
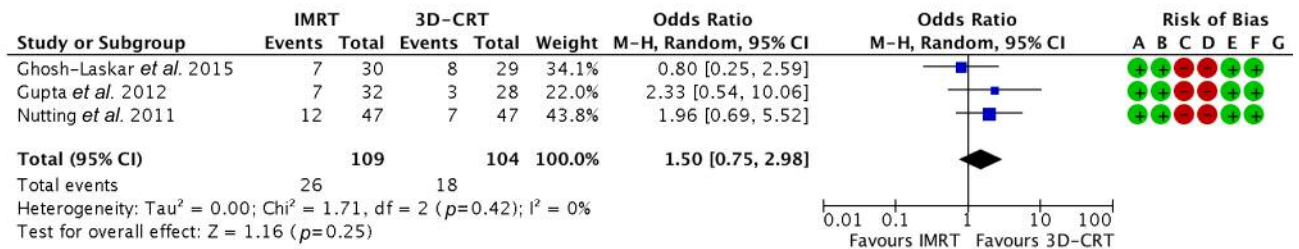


a



b



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 3. Forest plot of overall survival (a) and loco-regional control (b).

introduced in daily clinical practice. Optimizing future multimodal treatment for HNSCC requires collection of detailed toxicity data, both clinician-reported and patient-reported outcomes (PROs) (24). A plausible discordance between clinician and patient reporting of toxicity should be considered. For instance, patients in disease remission may have accepted moderate xerostomia, adjusting their expectation accordingly; whereas in other cases the same clinician-reported moderate RT toxicity may drastically impact patient quality of life. PROs inclusion in the rigorous toxicity reporting methods should be useful to provide additional information in decision making process.

In general, this meta-analysis provided additional contribution to published literature data, showing the superiority of IMRT over 3D-CRT in HNSCC patients management. Our main aim was to achieve the highest quality of research. The current meta-analysis was not a literature abstract-based meta-analysis. Conference

proceedings were not considered, due to the lack of statistical quality details and << given the variable evidence of concordance between conference abstracts and their subsequent full-text publications >>, as advised by the agency for healthcare research and quality (AHRQ) (25). All included studies were randomized clinical trials and addressed the same primary end-point and similar methods were used to evaluate xerostomia. The major limitation of the analysis was the relative limited number of trials. But trials' short time accrual period – ranged from 2003 to 2008 – may add homogeneity to results, even though the included trials did not record human papillomavirus (HPV) status. At present HPV evaluation is paramount in HNSCC risk stratification (26). Its positive status discriminates excellent prognosis disease from worst outcome in HPV-negative tumors. Future studies specifically designed and powered to test the benefit of IMRT over 3D-CRT based on HPV stratification and salivary glands-sparing RT approach would provide more

Table II. *Quality of evidence and strength of recommendation: Summary of findings. Intensity modulated radiotherapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT) in head and neck squamous cell carcinoma.*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 3D-CRT	Risk with IMRT				
OS assessed with: Kaplan–Meier product limit	40 per 100	32 per 100 (21 to 46)	OR=0.70 (0.39-1.24)	213 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,b,c}	
LRC assessed with: Kaplan–Meier product limit	17 per 100	24 per 100 (14 to 38)	OR=1.50 (0.75-2.98)	213 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,b,c}	
Acute xerostomia ≥2 assessed with: Cumulative incidence	76 per 100	54 per 100 (45 to 65)	RR=0.71 (0.59-0.86)	213 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,b,c}	
1-y xerostomia ≥2 assessed with: Cumulative incidence	59 per 100	27 per 100 (18 to 39)	RR=0.45 (0.31-0.65)	169 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,b,c}	
2-y xerostomia ≥2 assessed with: Cumulative incidence	55 per 100	14 per 100 (8 to 25)	RR=0.26 (0.15-0.46)	140 (3 RCTs)	⊕⊕⊕○ MODERATE ^{a,b,c}	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; LRC: loco-regional control; OR: odds ratio; OS: overall survival; RR: risk ratio. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. ^aMissing outcome data balanced across groups; ^bdetection bias; ^cmay not be downgraded.

conclusive evidence in term of clinical outcomes. We hoped to draw attention to the paucity of good quality data on this topic and improve the quality of future research.

Conclusion

This meta-analysis confirmed the efficacy of IMRT to reduce moderate to severe xerostomia onset, but cannot determine meaningful survival advantages in HNSCC. Prospective randomized trials aimed to compare IMRT *versus* 3D-CRT in an adequate homogeneous HNSCC population, with survival and main RT-related toxicities endpoints are necessary to definitely confirm IMRT value.

Conflicts of Interest

All Authors declare that they have no conflicts of interest that may be relevant to the contents of this manuscript.

Authors' Contributions

FDF, NP, PP have made substantial contributions to the conception of the work, the acquisition and interpretation of data and have drafted the work; OB, VT and AP have substantively revised it. All Authors have approved the submitted version.

References

- 1 National Comprehensive Cancer Network (NCCN). Guidelines Head and Neck Cancers, Version 2.2018. Available at: <http://www.nccn.org> (Last accessed 21/11/2019)
- 2 De Felice F, Musio D, Terenzi V, Valentini V, Cassoni A, Tombolini M, De Vincentiis M and Tombolini V: Treatment improvement and better patient care: which is the most important one in oral cavity cancer? *Radiat Oncol* 9: 263, 2014. PMID: 25479896. DOI: 10.1186/s13014-014-0263-x
- 3 Marta GN, Silva V, de Andrade Carvalho H, de Arruda FF, Hanna SA, Gadia R, da Silva JL, Correa SF, Vita Abreu CE and Riera R: Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. *Radiother Oncol* 110(1): 9-15, 2014. PMID: 24332675. DOI: 10.1016/j.radonc.2013.11.010
- 4 Gupta T, Kannan S, Ghosh-Laskar S and Agarwal JP: Systematic review and meta-analyses of intensity-modulated radiation therapy *versus* conventional two-dimensional and/or or three-dimensional radiotherapy in curative-intent management of head and neck squamous cell carcinoma. *PLoS One* 13(7): e0200137, 2018. PMID: 29979726. DOI: 10.1371/journal.pone.0200137
- 5 Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E and PARSPORT trial management group: Parotid-sparing intensity modulated *versus* conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre

- randomised controlled trial. *Lancet Oncol* 12(2): 127-136, 2011. PMID: 21236730. DOI: 10.1016/S1470-2045(10)70290-4
- 6 Rosenthal DI, Chambers MS, Fuller CD, Rebueno NC, Garcia J, Kies MS, Morrison WH, Ang KK and Garden AS: Beam path toxicities to non-target structures during intensity-modulated radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 72(3): 747-755, 2008. PMID: 18455324. DOI: 10.1016/j.ijrobp.2008.01.012
- 7 Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A and Agarwal J: Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. *Oral Oncol* 49(6): 634-642, 2013. PMID: 23562564. DOI: 10.1016/j.oraloncology.2013.02.013
- 8 Ghosh-Laskar S, Yathiraj PH, Dutta D, Rangarajan V, Purandare N, Gupta T, Budrukkar A, Murthy V, Kannan S and Agarwal JP: Prospective randomized controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: Long-term results. *Head Neck* 38: E1481-1487, 2016. PMID: 26561342. DOI: 10.1002/hed.24263
- 9 Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, Murthy V, Budrukkar A, Dinshaw K, Prabhaskar K, Chaturvedi P and D'Cruz A: Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: a randomized controlled trial. *Radiother Oncol* 104(3): 343-348, 2012. PMID: 22853852. DOI: 10.1016/j.radonc.2012.07.001
- 10 Moher D, Liberati A, Tetzlaff J, Altman DG and PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 62(10): 1006-1012, 2009. PMID: 25554246. DOI: 10.1186/2046-4053-4-1
- 11 Lefebvre C, Manheimer E and Glanville J: Chapter 6: Searching for studies. In: Higgins J, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org (Last accessed 21/11/2019)
- 12 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 31(5): 1341-1346, 1995. PMID: 7713792. DOI: 10.1016/0360-3016(95)00060-C
- 13 Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P and Schünemann HJ: GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 64(4): 383-394, 2011. PMID: 21195583. DOI: 10.1016/j.jclinepi.2010.04.026
- 14 Cochrane. Available at: <http://www.cochrane.org> (Last accessed 21/11/2019)
- 15 Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR: Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 8: 16, 2007. PMID: 17555582. DOI: 10.1186/1745-6215-8-16
- 16 Higgins JPT, Thompson SG, Deeks JJ and Altman DG: Measuring inconsistency in meta-analyses. *BMJ* 327: 557-560, 2003. PMID: 12958120. DOI: 10.1136/bmj.327.7414.557
- 17 De Felice F, Thomas C, Barrington S, Pathmanathan A, Lei M and Urbano TG: Analysis of loco-regional failures in head and neck cancer after radical radiation therapy. *Oral Oncol* 51(11): 1051-1055, 2015. PMID: 26506048. DOI: 10.1016/j.oraloncology.2015.08.004
- 18 De Felice F, Musio D, Bulzonetti N, Maghella F and Tombolini V: Target volume delineation based on diffusion-weighted magnetic resonance imaging for locally advanced head and neck cancer. *Anticancer Res* 36(8): 4181-4185, 2016. PMID: 27466529.
- 19 De Felice F, Musio D, Terenzi V, Valentini V, Cassoni A, Tombolini M, De Vincentiis M and Tombolini V: Treatment improvement and better patient care: which is the most important one in oral cavity cancer? *Radiat Oncol* 9: 263, 2014. PMID: 25479896. DOI: 10.1186/s13014-014-0263-x
- 20 Murdoch-Kinch CA, Kim HM, Vineberg KA, Ship JA and Eisbruch A: Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 72(2): 373-382, 2008. PMID: 18337023. DOI: 10.1016/j.ijrobp.2007.12.033
- 21 De Felice F, Musio D and Tombolini V: Osteoradionecrosis and intensity modulated radiation therapy: An overview. *Crit Rev Oncol Hematol* 107: 39-43, 2016. PMID: 27823650. DOI: 10.1016/j.critrevonc.2016.08.017
- 22 De Felice F, Thomas C, Patel V, Connor S, Michaelidou A, Sproat C, Kwok J, Burke M, Reilly D, McGurk M, Simo R, Lyons A, Oakley R, Jeannon JP, Lei M and Urbano TG: Osteoradionecrosis following treatment for head and neck cancer and the effect of radiotherapy dosimetry: the Guy's and St Thomas' Head and Neck Cancer Unit experience. *Oral Surg Oral Med Oral Pathol Oral Radiol* 122(1): 28-34, 2016. PMID: 27039003. DOI: 10.1016/j.oooo.2016.01.007
- 23 De Felice F, de Vincentiis M, Luzzi V, Magliulo G, Tombolini M, Ruoppolo G and Polimeni A: Late radiation-associated dysphagia in head and neck cancer patients: evidence, research and management. *Oral Oncol* 77: 125-130, 2018. PMID: 29362118. DOI: 10.1016/j.oraloncology.2017.12.021
- 24 Gilbert A, Ziegler L, Martland M, Davidson S, Efficace F, Sebagn Montefiore D and Velikova G: Systematic review of radiation therapy toxicity reporting in randomized controlled trials of rectal cancer: A comparison of patient-reported outcomes and clinician toxicity reporting. *Int J Radiat Oncol Biol Phys* 92(3): 555-567, 2015. PMID: 26068490. DOI: 10.1016/j.ijrobp.2015.02.021
- 25 Balshem H, Stevens A, Ansari M, Norris S, Kansagara D, Shamliyan T, Chou R, Chung M, Moher D and Dickersin K: Finding grey literature evidence and assessing for outcome and analysis reporting biases when comparing medical interventions: AHRQ and the effective health care program. Agency for healthcare research and Quality, AHRQ methods for effective health care, 2013. PMID: 24404628.
- 26 Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, Loomis AM and Shah JP: Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 67(2): 122-137, 2017. PMID: 28128848. DOI: 10.3322/caac.21389

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