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Proton Therapy for Nasopharyngeal Cancer: A Systematic Review

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Abstract **Original Research Article**

Nasopharyngeal cancer presents unique challenges due to its complex anatomical location and proximity to critical organs. This systematic review examines the relevance of proton therapy in treating nasopharyngeal cancer. Twenty-six articles met the inclusion criteria, comprising conceptual studies, practical evaluations of proton therapy, and assessments of acute toxicities. Proton therapy demonstrated comparable tumor conformation and lower doses to organs at risk (OARs) compared to intensity-modulated radiotherapy (IMRT). Preliminary evidence suggests that proton therapy is at least as effective as IMRT and may be less toxic. Proton therapy shows promise for primary treatment, boosting after photon therapy, salvage situations, and pediatric populations, but careful attention to OAR doses is crucial. However, large randomized clinical trials are needed to establish its superiority and assess long-term outcomes.

Keywords: Nasopharyngeal neoplasms, proton therapy, intensity modulated proton therapy (IMPT), intensity modulated radiotherapy (IMRT), organs at risk (OAR).

INTRODUCTION

Nasopharyngeal cancer is aradiosensitive disease and is characterized by a complex anatomical configuration. Its deep-seated anatomy and its proximity to many organs at risk such as the brainstem, cranial nerves, orbit and optic nerves, temporal lobes and the constrictors muscles of the pharynx and masticators,doesn'tallow surgery in most cases(Maingon *et al.*, 2016). The reference treatment is radiotherapy, often potentiated by chemotherapy (from stage II)(Grégoire *et al.*, 2015; Ribassin-Majed *et al.*, 2017). But its location in head and neck compartmentis associated with several rays acute and late toxicities, specially with 3D conformal therapy(Trotti *et al.*, 2003). These toxicities have been addressed to some extent with photon intensity-modulated radiotherapy (IMRT), but late toxicities such as consistent xerostomia and dysphagia remain a significant concern(Langendijk *et al.*, 2008). Proton therapy, by virtue of the Bragg-Peak phenomenon, seems to offer more favorable dosimetric profiles compared to other photon-based radiotherapy techniques, including IMRT, in many cancer types (Mitin & Zietman, 2014).This technique capitalizes on the sharp dose fall-off at the tumor edge, allowing a remarkable reduction in the dose delivered to adjacent normal tissues, particularly with intensity-modulated proton therapy (IMPT). IMPT has been advocated as a promising radiation technique that could potentially reduce toxicity to protect organs at risk (OAR) and provide opportunities for dose escalation in the tumor area(Blanchard *et al.*, 2018).

Moreover, although proton therapy is still not a routine technique in the management of nasopharyngeal cancer, its utilization is increasing, with a rapid rise in the number of proton centers worldwide, not only in the USA (Leeman *et al.*, 2017).

The aim of this systematic review is to clarify the relevance of proton therapy in the treatment of nasopharyngeal cancer.

MATERIAL AND METHODS

The systematic review was conducted using PubMed as the primary database. The search strategy involved utilizing specific Mesh terms, identified by Hetop, namely "nasopharyngeal neoplasms" AND "proton therapy," to identify relevant articles. The inclusion criteria for article selection were limited to those available in full text.

Following the initial search, all abstracts of the identified articles were meticulously reviewed. Articles that were determined to be directly relevant to the subject matter of the review were retained for further analysis. Conversely, articles that were considered too general or lacked relevance to the specific topic were excluded from the study.

Subsequently, the full text of the selected papers was obtained and carefully examined to extract the relevant data and insights. The comprehensive reading of these papers allowed for a detailed evaluation of the methodology employed, the study design, the outcomes reported, and any limitations identified.

By adhering to a rigorous methodology and utilizing the available resources, the systematic review aimed to provide a comprehensive and reliable synthesis of the existing literature on the use of proton therapy for nasopharyngeal neoplasms.

RESULTS

A total of 41 articles were generated, all of which were published between 2002 and 2023. One article was eliminated due to the absence of an available abstract. Fourteen articles were not retained because their major topics were not specific enough to the chosen subject. For instance, the first article addressed the possibility of generating synthetic images from MR images for intensity-modulated proton therapy treatment planning of nasopharyngeal cancer (Chen *et al.,* 2022), which deviated too far from the topic of this review. The remaining thirteen articles primarily focused on dosimetric and radiobiological considerations, which were too general for the technique and not specific to the pathology.

Therefore, a total of twenty-six papers met the inclusion criteria. No large randomized clinical trials were found, and only retrospective studies, small cohorts and two reviews were published.

The topics covered in these articles could generally be categorized into three main groups. The first category pertained to conceptual subjects that linked proton radiobiology to the challenges of tumoricidal irradiation of the nasopharynx with minimal sequelae. The second category focused on practical aspects, evaluating the effectiveness of proton therapy, often in comparison to IMRT, as a primary treatment and in cases of recurrence. The last category specifically addressed acute toxicities caused by proton therapy in nasopharyngeal neoplasms. However, this topic was also analyzed in all the identified cohorts simultaneously with clinical outcomes.

Conceptual studies have been reported, based on the comparison of treatment planning between proton beam therapy and IMRT for patients with newly diagnosed and recurrent nasopharyngeal carcinoma. The objective of these studies was to evaluate the potential benefits and limitations of both treatment modalities. The findings of these studies indicate that both proton beam therapy and IMRT achieved comparable levels of tumor conformation while significantly reducing the radiation dose to the OAR. This reduction in radiation dose to the OAR is believed to contribute to decreased morbidity and improved quality of life for patients(Lewis *et al.,* 2016; Liu *et al.,* 2010; Noël *et al.,* 2002; Taheri-Kadkhoda *et al.,* 2008).

To start with, in 2015, Steven J. Frank (Frank, 2016)discussed the toxic effects associated with intensity-modulated photon radiation therapy for head and neck cancer. Proton therapy, particularly multifield optimization IMPT, has been established as a safe and effective alternative for treating head and neck tumors (Holliday & Frank, 2014). Studies have shown that IMPT provides improved dose distribution, reducing the need for gastrostomy tubes and minimizing side effects (Frank *et al.,* 2013; Holliday *et al.,* 2015; Hutcheson *et al.,* 2013). IMPT holds the potential to be a disruptive innovation in managing head and neck tumors, but further evidence and considerations are needed (Goitein & Cox, 2008).

About a year later, Emma B. Holliday and al. dedicated a paper to the proton therapy in nasopharyngeal neoplasms. She treated the evidence of dosimetric advantages, the clinical benefit through series that will be cited on the corpus of this review, with a word on treatment planning and delivery, encouraging similarly opening prospective clinical trials so that high-quality evidence can be collected to better use this form of treatment for patients in the future (Holliday & Frank, 2016).

In 2019, a paper updated the subject, and concluded that proton therapy offers advantages in head and neck cancer treatment, including reduced doses to normal tissues and potential dose escalation in the tumor area in nasopharyngeal neoplasms. IMPT has demonstrated better sparing of normal tissues compared to IMRT, such as the spinal cord, parotid glands, and larynx/esophagus. But the same observation was noted : further research is needed to explore dosimetric superiority, in vivo verification, and conduct comparative studies with IMRT(Sun *et al.,* 2019).

These findings lead us to published cohort results. Thus,the Jama Network Open article (Falchook, 2021) edited an article that reported the results of a retrospective study comparing IMPT and IMRT in the treatment of head and neck cancer. The study found no statistically significant differences in loco-regional failure-free survival, progression-free survival, distant metastasis-free survival, or overall survival between the two techniques (Li *et al.,* 2021). Both IMPT and IMRT were highly effective at achieving disease control, and

reducing toxicities emerged as a key aspect of improving treatment outcomes.

Adaptive IMPT was investigated in two studies. The first study by Hideki Minatogawa *et al.,* (Minatogawa *et al.,* 2021) demonstrated that the adaptive approach enhanced the potential benefit of IMPT over IMRT, resulting in reduced doses to OAR and potentially reducing adverse effects. The second study highlighted the robust target coverage and acceptable OAR dose variation achieved through optimized IMPT plans combined with volumetric verification imaging and adaptive planning (Scandurra *et al.,* 2022).

Proton therapy has also been explored for boosting tumor treatment after an initial series with photons. A French cohort study at the Curie Institute showed that complementary proton therapy delivered a similar or even better toxicity profile compared to IMRT alone, along with comparable local control outcomes, particularly for T4N0M0 nasopharyngeal carcinoma (Beddok *et al.,* 2019). And a more recent Italian cohort study demonstrated that sequential proton boost resulted in significantly lower acute toxicity profiles compared to a full course of IMRT, with similar two-year disease-related outcomes (progression-free survival and progression-free survival) (Alterio *et al.,* 2020).

Lastly, it was interesting to propose proton therapy for the management of recurrences. And Hing Ming Hung *et al.,* (Hung *et al.,* 2022) showed a dosimetric advantages of Intensity Modulated Proton Therapy over Intensity Modulated Radiotherapy in terms of coverage of target volume and sparing of neurological organs-at-risk in salvaging recurrent nasopharyngeal carcinoma, but with high doses to carotid artery and nasopharyngeal mucosa, which are associated with potential carotid blowout and massive epistaxis. This paper warned on the necessity to be rigorous to the doses at these organs, which was not always assured with protons. The analyze of a sub group of seven patients of a Korean study who were re irradiated by IMPT at the recurrence showed a similar rate of overall survival, local free survival and toxicity free survival with IMRT, and suggested that this technique was feasible in treating locally recurrent disease (Nam *et al.,* 2022).

Pediatric patients with non-metastatic nasopharyngeal neoplasms were also considered in a cohort and two reported cases. The first one treated these patients with induction chemotherapy followed by moderate-dose proton therapy(Uezono *et al.,* 2019). Overall survival, progression-free survival, and local control rates were 100% at 3 years. Serious late side effects included cataract, esophageal stenosis requiring dilation, sensorineural hearing loss requiring aids, and hormone deficiency, concluding that moderate-dose proton therapy could potentially reduce toxicity in the brain and skull base region without compromising disease control, but with the necessity to evaluate any reduction in long-term complications with a further follow up. On the other hand, the two cases reported a total remission from the disease and few late toxicities (right parotid gland smaller than the left gland, and right lower back teeth showed atrophy, grade 1 trismus, retardation on parotids, mandibular ramus and cervical spine in the treatment field) but no xerostomia or facial deformation (Oshiro *et al.,* 2011).

Acute toxicities were the major topics of two papers. The first one was a general paper in nasopharynx and paranasal sinus cancers, and showed a decreased dose at OAR with IMPT. For example, in node negative, oral cavity received 5.1 Gy versus 31.5Gy with IMRT.None of the patients required the placement of gastrostomy tube at the time of treatment and IMPT was associated with a lower opioid pain requirement at the completion of radiation and a lower rate of gastrostomy tube dependence by the completion of radiation therapy and at 3 months after radiation(McDonald *et al.,* 2016). The second paper was an observational study that investigated the prognostic factors and treatment outcomes of acute radiation dermatitis among fifty-seven patients with nasopharyngeal carcinoma treated with IMPT. The results showed this toxicity is a major concern for these patients, especially those with habitual smoking or advanced nodal status (Fang *et al.,* 2023). Only topical corticosteroid, silver sulfadiazine, and non-adhering silicone dressing were used.

DISCUSSION

The analysis of the corpus revealed a collection of 41 articles published between 2002 and 2023, with a wide range of topics related to proton therapy in nasopharyngeal neoplasms. However, it is important to note that the majority of the studies were based on retrospective designs or small cohorts, which may limit the generalizability of the findings and introduce potential biases.

While some studies highlighted the conceptual aspects of proton therapy and its potential benefits in achieving tumoricidal irradiation with minimal sequelae, the evidence supporting these claims was often limited. Additionally, the practical comparisons between proton therapy and intensity-modulated radiation therapy (IMRT) lacked robust evidence from large randomized clinical trials.

The corpus included studies that emphasized the dosimetric advantages of proton therapy, such as reduced radiation dose to organs at risk and improved target coverage. However, the clinical significance of these dosimetric improvements and their impact on patient outcomes remained unclear. Furthermore, the long-term complications and late toxicities associated with proton therapy were not thoroughly addressed,

highlighting the need for further research and longer follow-up periods.

The limited number of large-scale randomized clinical trials addressing proton therapy in nasopharyngeal neoplasms is a significant limitation. This scarcity of high-quality evidence makes it challenging to draw definitive conclusions about the superiority of proton therapy over other treatment modalities, such as IMRT. Future research efforts should focus on conducting well-designed prospective studies with larger sample sizes to provide more reliable and robust evidence.

In summary, while the corpus of articles on proton therapy in nasopharyngeal neoplasms presented some promising findings regarding tumor conformation and organ-at-risk sparing, it is crucial to approach the results with caution due to the limitations of the available evidence. Further research, including rigorous randomized controlled trials and long-term follow-up studies, is needed to better understand the true clinical benefits, potential toxicities, and overall efficacy of proton therapy in this specific context.

CONCLUSION

In conclusion, the corpus of articles on proton therapy in nasopharyngeal neoplasms highlights the potential benefits of this treatment modality in terms of tumor conformation and reduced radiation dose to organs at risk. However, the evidence primarily consists of retrospective studies, small cohorts, and case studies, limiting its generalizability. Comparative studies with intensity-modulated radiation therapy (IMRT) and large-scale randomized controlled trials are needed to establish the efficacy and long-term outcomes of proton therapy. Further research is necessary to fully understand its potential advantages and limitations in improving patient outcomes.

REFERENCES

- Alterio, D., D'Ippolito, E., Vischioni, B., Fossati, P., Gandini, S., Bonora, M., Ronchi, S., Vitolo, V., Mastella, E., Magro, G., Franco, P., Ricardi, U., Krengli, M., Ivaldi, G., Ferrari, A., Fanetti, G., Comi, S., Tagliabue, M., Verri, E., … & Orecchia, R. (2020). Mixed-beam approach in locally advanced nasopharyngeal carcinoma: IMRT followed by proton therapy boost versus IMRT-only. Evaluation of toxicity and efficacy. *Acta Oncologica*, *59*(5), 541–548. https://doi.org/10.1080/0284186X.2020.1730001
- Beddok, A., Feuvret, L., Noël, G., Bolle, S., Deberne, M., Mammar, H., Chaze, A., Le Tourneau, C., Goudjil, F., Zefkili, S., Herman, P., Dendale, R., & Calugaru, V. (2019). Complément de dose de protons pour les cancers du nasopharynx localement évolués: Une expérience de l'institut Curie. *Cancer/Radiothérapie*, *23*(4), 304–311. https://doi.org/10.1016/j.canrad.2019.01.003
- Blanchard, P., Gunn, G. B., Lin, A., Foote, R. L., Lee, N. Y., & Frank, S. J. (2018). Proton Therapy for Head and Neck Cancers. *Seminars in Radiation Oncology*, *28*(1), 53–63. https://doi.org/10.1016/j.semradonc.2017.08.004
- Chen, S., Peng, Y., Qin, A., Liu, Y., Zhao, C., Deng, X., Deraniyagala, R., Stevens, C., & Ding, X. (2022). MR-based synthetic CT image for intensity-modulated proton treatment planning of nasopharyngeal carcinoma patients. *Acta Oncologica*, *61*(11), 1417–1424. https://doi.org/10.1080/0284186X.2022.2140017
- Falchook, A. (2021). Intensity-Modulated Radiation Therapy and Intensity-Modulated Proton Therapy—2 Effective Treatment Modalities for Nasopharyngeal Cancer. *JAMA Network Open*, *4*(6), e2113650. https://doi.org/10.1001/jamanetworkopen.2021.13650
- Fang, K., Lee, C., Chuang, H., Huang, T., Chien, C., Tsai, W., & Fang, F. (2023). Acute radiation dermatitis among patients with nasopharyngeal carcinoma treated with proton beam therapy: Prognostic factors and treatment outcomes. *International Wound Journal*, *20*(2), 499–507. https://doi.org/10.1111/iwj.13897
- Frank, S. J. (2016). Intensity Modulated Proton Therapy for Head and Neck Tumors: Gilding the Lily or Holy Grail? *International Journal of Radiation Oncology*Biology*Physics*, *95*(1), 37–39. https://doi.org/10.1016/j.ijrobp.2015.12.377
- Frank, S. J., Rosenthal, D. I., Ang, K., Sturgis, E. M., Chambers, M. S., Gunn, G. B., Hutcheson, K. A., Zhu, X. R., Palmer, M. B., & Garden, A. S. (2013). Gastrostomy Tubes Decrease by Over 50% with Intensity Modulated Proton Therapy (IMPT) During the Treatment of Oropharyngeal Cancer Patients: A Case–Control Study. *International Journal of Radiation Oncology*Biology*Physics*, *87*(2), S144. https://doi.org/10.1016/j.ijrobp.2013.06.371
- Goitein, M., & Cox, J. D. (2008). Should Randomized Clinical Trials Be Required for Proton Radiotherapy? *Journal of Clinical Oncology*, *26*(2), 175–176. https://doi.org/10.1200/JCO.2007.14.4329
- Grégoire, V., Langendijk, J. A., & Nuyts, S. (2015). Advances in Radiotherapy for Head and Neck Cancer. *Journal of Clinical Oncology*, *33*(29), 3277–3284. https://doi.org/10.1200/JCO.2015.61.2994
- Holliday, E. B., & Frank, S. J. (2014). Proton Radiation Therapy for Head and Neck Cancer: A Review of the Clinical Experience to Date. *International Journal of Radiation Oncology*Biology*Physics*, *89*(2), 292–302. https://doi.org/10.1016/j.ijrobp.2014.02.029

- Holliday, E. B., & Frank, S. J. (2016). Proton therapy for nasopharyngeal carcinoma. *Chinese Clinical Oncology*, *5*(2), 25–25. https://doi.org/10.21037/cco.2016.03.05
- Holliday, E. B., Garden, A. S., Rosenthal, D. I., Fuller, C. D., Morrison, W. H., Gunn, G. B., Phan, J., Beadle, B. M., Zhu, X. R., Zhang, X., Hanna, E., Glisson, B. S., Hutcheson, K. A., El-Naggar, A. K., Hong, J.-H., Hung, T.-M., Uzel, E. K., Lewis, G., & Frank, S. J. (2015). Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy. *International Journal of Particle Therapy*, *2*(1), 19–28. https://doi.org/10.14338/IJPT-15-00011.1
- Hung, H. M., Chan, O. C. M., Mak, C. H., Hung, W. M., Ng, W. T., & Lee, M. C. H. (2022). Dosimetric comparison of intensity modulated radiotherapy and intensity modulated proton therapy in the treatment of recurrent nasopharyngeal carcinoma. *Medical Dosimetry*, *47*(1), 14–19. https://doi.org/10.1016/j.meddos.2021.07.002
- Hutcheson, K., Lewin, J. S., Garden, A. S., Rosenthal, D. I., Weber, R. S., William, W. N., Gunn, G. B., Morrison, W. H., Fuller, C. D., & Frank, S. J. (2013). Early Experience With IMPT for the Treatment of Oropharyngeal Tumors: Acute Toxicities and Swallowing-Related Outcomes. *International Journal of Radiation Oncology*Biology*Physics*, *87*(2), S604. https://doi.org/10.1016/j.ijrobp.2013.06.1597
- Langendijk, J. A., Doornaert, P., Verdonck-de Leeuw, I. M., Leemans, C. R., Aaronson, N. K., & Slotman, B. J. (2008). Impact of Late Treatment-Related Toxicity on Quality of Life Among Patients With Head and Neck Cancer Treated With Radiotherapy. *Journal of Clinical Oncology*, *26*(22), 3770–3776. https://doi.org/10.1200/JCO.2007.14.6647
- Leeman, J. E., Romesser, P. B., Zhou, Y., McBride, S., Riaz, N., Sherman, E., Cohen, M. A., Cahlon, O., & Lee, N. (2017). Proton therapy for head and neck cancer: Expanding the therapeutic window. *The Lancet Oncology*, *18*(5), e254–e265. https://doi.org/10.1016/S1470-2045(17)30179-1
- Lewis, G. D., Holliday, E. B., Kocak-Uzel, E., Hernandez, M., Garden, A. S., Rosenthal, D. I., & Frank, S. J. (2016). Intensity-modulated proton therapy for nasopharyngeal carcinoma: Decreased radiation dose to normal structures and encouraging clinical outcomes: IMPT for NASOPHARYNGEAL CARCINOMA. *Head & Neck*, *38*(S1), E1886–E1895. https://doi.org/10.1002/hed.24341
- Li, X., Kitpanit, S., Lee, A., Mah, D., Sine, K., Sherman, E. J., Dunn, L. A., Michel, L. S., Fetten, J., Zakeri, K., Yu, Y., Chen, L., Kang, J. J., Gelblum, D. Y., McBride, S. M., Tsai, C. J., Riaz, N., & Lee, N. Y. (2021). Toxicity Profiles and Survival Outcomes Among Patients With Nonmetastatic Nasopharyngeal Carcinoma Treated With Intensity-Modulated Proton Therapy vs Intensity-Modulated Radiation Therapy. *JAMA Network Open*, *4*(6), e2113205. https://doi.org/10.1001/jamanetworkopen.2021.13205
- Liu, S.-W., Li, J.-M., Chang, J.-Y., Yu, J.-M., Chen, Q., Jiang, Q.-A., Mu, X.-K., Zhao, M.-H., Tian, Y., & Wei, Q.-L. (2010). A treatment planning comparison between proton beam therapy and intensity-modulated x-ray therapy for recurrent nasopharyngeal carcinoma. *Journal of X-Ray Science and Technology*, *18*(4), 443–450. https://doi.org/10.3233/XST-2010-0265
- Maingon, P., Blanchard, P., Bidault, F., & Calmels, L. (2016). Radiothérapie des cancers du nasopharynx. *Cancer/Radiothérapie*, *20*, S104–S109. https://doi.org/10.1016/j.canrad.2016.07.031
- McDonald, M. W., Liu, Y., Moore, M. G., & Johnstone, P. A. S. (2016). Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: Cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. *Radiation Oncology*, *11*(1), 32. https://doi.org/10.1186/s13014-016-0600-3
- Minatogawa, H., Yasuda, K., Dekura, Y., Takao, S., Matsuura, T., Yoshimura, T., Suzuki, R., Yokota, I., Fujima, N., Onimaru, R., Shimizu, S., Aoyama, H., & Shirato, H. (2021). Potential benefits of adaptive intensity-modulated proton therapy in nasopharyngeal carcinomas. *Journal of Applied Clinical Medical Physics*, *22*(1), 174–183. https://doi.org/10.1002/acm2.13128
- Mitin, T., & Zietman, A. L. (2014). Promise and Pitfalls of Heavy-Particle Therapy. *Journal of Clinical Oncology*, *32*(26), 2855–2863. https://doi.org/10.1200/JCO.2014.55.1945
- Nam, H., Ahn, Y. C., Yang, K., Oh, D., & Noh, J. M. (2022). Re-irradiation with Moderate Hypo-fractionation Using Intensity Modulated Photon or Proton Radiation Therapy in Locally Recurrent Squamous Cell Carcinoma of Nasopharynx. *Cancer Research and Treatment*, *54*(1), 96–108. https://doi.org/10.4143/crt.2020.1349
- Noël, G., Boisserie, G., Dessard-Diana, B., Ferrand, R., Hasboun, D., Gasowski, M., Desblancs, C. L., Simon, J. M., Baillet, F., & Mazeron, J. J. (2002). Comparaison par les histogrammes dose-volume de deux techniques d'irradiation conformationnelle des cancers du nasopharynx classés T4N0M0, l'une par photons et protons et l'autre par photons seuls. *Cancer/Radiothérapie*, *6*(6), 337–348. https://doi.org/10.1016/S1278-3218(02)00222-6
- Oshiro, Y., Sugahara, S., Fukushima, T., Okumura, T., Nakao, T., Mizumoto, M., Hashimoto, T., Tsuboi, K., Kaneko, M., & Sakurai, H. (2011).

Pediatric nasopharyngeal carcinoma treated with proton beam therapy. Two case reports. *Acta Oncologica*, *50*(3), 470–473. https://doi.org/10.3109/0284186X.2010.509106

- Ribassin-Majed, L., Marguet, S., Lee, A. W. M., Ng, W. T., Ma, J., Chan, A. T. C., Huang, P.-Y., Zhu, G., Chua, D. T. T., Chen, Y., Mai, H.-Q., Kwong, D. L. W., Cheah, S.-L., Moon, J., Tung, Y., Chi, K.-H., Fountzilas, G., Bourhis, J., Pignon, J. P., … & on behalf of the Meta-Analysis of Chemotherapy in Nasopharyngeal Collaborative Group. (2017). What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis. *Journal of Clinical Oncology*, *35*(5), 498–505. https://doi.org/10.1200/JCO.2016.67.4119
- Scandurra, D., Meijer, T. W. H., Free, J., Van Den Hoek, J. G. M., Kelder, L., Oldehinkel, E., Steenbakkers, R. J. H. M., Both, S., & Langendijk, J. A. (2022). Evaluation of robustly optimised intensity modulated proton therapy for nasopharyngeal carcinoma. *Radiotherapy and Oncology*, *168*, 221–228. https://doi.org/10.1016/j.radonc.2022.01.043
- Sun, X.-S., Li, X.-Y., Chen, Q.-Y., Tang, L.-Q., & Mai, H.-Q. (2019). Future of Radiotherapy in Nasopharyngeal Carcinoma. *The British Journal of Radiology*, *92*(1102), 20190209. https://doi.org/10.1259/bjr.20190209
- Taheri-Kadkhoda, Z., Björk-Eriksson, T., Nill, S., Wilkens, J. J., Oelfke, U., Johansson, K.-A., Huber, P. E., & Münter, M. W. (2008). Intensity-modulated radiotherapy of nasopharyngeal carcinoma: A comparative treatment planning study of photons and protons. *Radiation Oncology*, *3*(1), 4. https://doi.org/10.1186/1748-717X-3-4
- Trotti, A., Bellm, L. A., Epstein, J. B., Frame, D., Fuchs, H. J., Gwede, C. K., Komaroff, E., Nalysnyk, L., & Zilberberg, M. D. (2003). Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: A systematic literature review. *Radiotherapy and Oncology*, *66*(3), 253–262. https://doi.org/10.1016/S0167-8140(02)00404-8
- Uezono, H., Indelicato, D. J., Rotondo, R. L., Sandler, E. S., Katzenstein, H. M., Dagan, R., Mendenhall, W. M., Mailhot Vega, R., Brennan, B. M., & Bradley, J. A. (2019). Proton therapy following induction chemotherapy for pediatric and adolescent nasopharyngeal carcinoma. *Pediatric Blood & Cancer*, *66*(12). https://doi.org/10.1002/pbc.27990