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Envisioning an Italian Head and Neck Proton Therapy Model-Based Selection: Challenge and Opportunity

Introduction

Radiation therapy (RT) plays a crucial role in managing head and neck cancer (HNC) patients, either alone or as part of a multimodal approach that includes surgery and systemic therapy.[1,2] In both definitive and adjuvant settings, intensity-modulated RT (IMRT) represents the more advanced photon-based and current standard RT technique. It has led to a significant improvement in radiation-induced toxicity profiles compared to older RT techniques, without compromising clinical outcomes. Nonetheless, toxicity rates remain relevant, especially for advanced clinical stages, with substantial long-term consequences impacting on quality of life (QOL), due to the fact that normal tissues inevitably receive exit doses from photons. Moreover, patients with HNC face a non-negligible risk of developing secondary primary cancers, especially in the head and neck area and lungs.[3] In addition, the rise in the incidence of human papillomavirus associated to oropharyngeal squamous cell carcinoma (HPV-OPC), mainly diagnosed in middle age patients and with more favorable prognosis, emphasizes the importance of minimizing treatment-related side effects.[4-7] In this scenario, the advent of proton therapy (PT) marks a new era. Indeed, the advantages of PT rely on the intrinsic dose deposition curve, capable of maximizing the dose to the tumor at the so-called Bragg peak, with significantly higher sparing of the surrounding organs at risk compared to photons.[8] On the other hand, radiobiological effectiveness is comparable with a fixed radiobiological effectiveness value of 1.1, currently recommended and adopted worldwide in PT.[9,10] According to the most updated survey on current practices among European PT centers, data have shown that adult patients are submitted to PT if the main objective is to decrease toxicity risk or, more rarely, to escalate the dose for increasing tumor control.[11]

Although the current clinical evidence for PT is mainly based on retrospective studies that report advantages in toxicity reduction without compromising tumor control[12] or even showing statistically superior outcomes compared to photon-based RT in definitive HNC patients,[13] the magnitude of this benefit is likely largely attributed to fewer sequelae at 2 to 4 years, coupled with the high quality of planning and delivery in PT, especially considering new active scanning technologies.[14,15]

More recently, an initial analysis of the MD Anderson-led phase III study (IMRT vs IMPT) on oropharyngeal cancer (NCT01893307) reported that PT was not inferior in terms of progression-free survival compared to IMRT, with a potential protective role in overall survival and a reduction in feeding tube dependence.[16,17]

Other prospective randomized controlled trials (RCTs) comparing IMRT and PT are currently ongoing, essentially with the primary endpoint being toxicity/QOL (NCT03829033; ISRCTN: 16424014 [TORPEDO]). Considering the current evidence and pending the results of RCTs, several issues are under discussion within the radiation oncology community. These range from methodology for obtaining clinical evidence, with emphasis on the utility of prospective international registries, to adequate patient selection integrating PT economic issues. Nevertheless, a careful evaluation of the actual cost-effectiveness of PT over IMRT should take into account each country's peculiarities such as the clinical expertise, the geographical distribution of patients, as well as the impact of treatments on health-related QOL.

In general, photon-based treatments are more widespread, established, and less expensive, hence allowing for the highest availability, minimal training, societal and clinical confidence, along with overall convenience across countries. The model-based selection (MBS) approach from the Netherlands has been introduced as an evidence-based methodology with nuanced perspectives on patient selection and clinical validation beyond traditional RCTs.[18] It is grounded on normal tissue complication probability (NTCP) models,[19] which have been externally validated in independent photon-based cohorts to predict severe and impairing radiation-induced side effects in HNC patients. With these principles, the NTCP-MBS was implemented in Northern Europe to select patients for either definitive photon-RT or PT and it has been under exploration for approximately six years, demonstrating its clinical safety and feasibility.[20] Since October 2017, the National Indication Protocol for HNC PT (NIPP-HNC) was formally approved and adopted in the Netherlands to select patients for PT.[21]

In the Italian scenario, the Italian Association for Radiotherapy and Clinical Oncology (Associazione Italiana di Radioterapia e Oncologia Clinica [AIRO]) followed and supported the development of PT since the very beginning, with documents that reported the potential indications for proton treatments based on the clinical and scientific evidence.[22] Since 2004,[23] the scientific literature has been enquired, and coupled with the Italian oncological incidence, to estimate the actual need of PT centers. After later literature revisions, at least 5 centers for PT (equipped with 2-4 treatment rooms) were recommended, with a well-balanced geographical and demographical distribution.[24] Currently, in Italy, three facilities are dedicated to deliver PT and others are in a planning phase.[25] However, definitive selection guidelines for PT of HNC patients are yet to be established.

The aim of our manuscript was to analyze the main aspects involved in the implementation of a MBS strategy for HNC candidates for definitive RT in relation to the Italian landscape, as well as exploring its feasibility and sustainability.

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Head and neck cancer model-based selection: The Northern Europe experience

In Northern Europe, the Netherlands was the first and only country to have established in clinics a MBS for selecting HNC patients for PT over photon-RT.[18] The foundation of the Dutch NTCP-MBS approach was the establishment of NIPP-HNC[21] thanks to multidisciplinary efforts, combining scientific (proton, photon-RT, and clinical epidemiology experts), national health care, and insurance parties. The radiation-induced toxicities of interest were selected with respect to the impact on the QOL and prevalence in HNC. The NTCP models were evaluated accordingly, and selected based on their quality and robustness. Hence, the structured tumor data to feed NTCP models are uniformly provided by the Dutch National Proton Registry.[26,27] The Dutch Society for Radiotherapy and Oncology sets the cut-off for the NTCP difference (ΔNTCP) based on the severity and consequent QOL reduction, as well as strictly considering the proportion of patients selected for PT. Finally, processes involving the national platforms specialized for PT and HNC RT and the other stakeholders led the National Health Care Institute to include the MBS into the national insurance basic package.

Similarly in Denmark, the six Danish Head and Neck Cancer centers (DAHANCA) set up a clinical trial to evaluate PT over photon-RT (NCT04607694), randomizing eligible HNCs after a preselection based on the potential NTCP advantage of PT.[28] A nonrandomized feasibility trial was successfully conducted between 2019 and 2020 to explore the logistic, social, financial, and clinical sustainability of the approach (NCT05423704). Comprehensive training and technical support were provided by the DAHANCA quality assurance group to local photon-RT centers to first evaluate candidate HNCs. The average technical treatment delay, due to NTCP evaluation, was clinically acceptable, and most of the selected patients accepted the PT referral, regardless of geographical provenience. The ΔNTCP was set arbitrarily and underwent changes over time to optimize the enrollment process.[29]

Envisioning the Italian model-based selection strategy

A schematic proposal of NTCP-MBS in Italy and interplay between variables involved is depicted in Figure 1. A comparison between the Netherlands, Denmark, and Italy with respect to the MBS most impactful factors is reported in Table 1. Substantial differences emerged between the Italian and Dutch scenarios, presenting the MBS as a challenge despite being a potentially relevant clinical and socio-economic achievement. The need for rigorous strategies to select HNC patients for PT is of great importance in Italy, considering that the Italian population is roughly three times the population of Denmark with particular HNC incidence,[30] which has been using NTCP model-based selection for years.

Italian head and neck cancer model-based selection: Scientific, clinical, technical, and socio-economic design and challenges

In the Dutch experience, the core root of NIPP-HNC was the expert working group. Within AIRO, there is currently neither a network nor a dedicated working group for PT. This could be desirable given the future development of this technology in Italy, also to compare with European groups. This network, mentored by the international PT community, could be responsible for various tasks, with the implementation of MBS as the first milestone. In the HNC landscape, this Italian PT network would provide guidance to the AIRO HNC working group and other major HNC Italian associations in designing scientifically comprehensive MBS guidelines and protocols. The scientific premise of this approach relies on the analysis of the HNC radiation-induced toxicity prevalence, the availability of dedicated NTCP models, and the evaluation of model robustness and consistency in the Italian landscape, eventually supported by satellite ad hoc clinical (and/or in-silico) trials as well as new NTCP model development.[34,35]

From a technical perspective, the identification of a strategic photon-RT department for each Italian region (*Regional PT Referral Hub*) would facilitate the MBS process, acting as a reference point for local photon-RT facilities and a link with the national PT centers. The establishment of such hierarchical MBS management is envisioned due to the high number (ie, 186) of widespread Italian photon-RT facilities.[36] PT technical expertise and support should be formally provided to the *Regional PT Referral Hub* team, including easy-to-use tools (eg, NTCP modules[37,38]), dedicated training, and indications for HNC PT preselection (eg,workshops, conferences). The *Regional PT Referral Hub* team will include trained radiation oncologists and medical physicists, supported by case managers, bioengineers, data managers, information technology (IT) specialists, and other technical personnel. Such a team will help disseminate PT awareness, provide preselection guidelines, and performe formal periodic audits. In such Italian MBS setting, PT would become a shared national resource, supported by a solid centralized health care IT infrastructure toward reliable, faster, and safer data transfer to prevent treatment time delays. In this context, the establishment and widespread of a centralized electronic medical record (EMR) will play a key role. A uniform and adequate dataset will be defined in compliance with national and European data regulation procedures, providing all the needed information for the MBS toxicity prediction as well as tracking follow-up data toward prospective updates of the NTCP models. Such an envisioned scientific, clinical, and technical framework is schematically represented in Figure 2.

In 2017, the Italian Ministry of Public Health reviewed the so-called *Essential Assistance Levels*, establishing a list of 10 clinical elective indications for hadrontherapy which can be reimbursed by the public national health system (NHS) with specific fares. Nonetheless, the expenses for PT are borne directly by the PT facilities and only reimbursed afterward. The envisioned MBS protocol should be embedded in the essential assistance levels, allowing for efficient and economically sustainable patient management from PT facilities. Furthermore, a logistic and economic support framework should be established for patients coming from distant regions, actually provided only in a few cases by the PT centers. In the present Italian landscape, the geographical, socio-economic, and health status will likely result in severe imbalances in PT access considering that, at present, PT facilities are all located in Northern Italy with a higher rate of PT referral refusal expected in Southern Italy, especially for patients with impaired health and weak social status. Both clinical and economical failure will then arise, with patients receiving suboptimal treatments and the NHS dispersing time and resources in the MBS selection processes.

Cost-effectiveness of model-based selection in head and neck cancer

Cost-effectiveness studies typically assess the incremental cost-effectiveness ratio (ICER) of a given procedure compared to alternative treatment strategies, that is, the incremental cost associated with a quality-adjusted life year gained. Literature studies investigating the economic burden of PT in HNC reported, from a payer perspective, the highest cost-effectiveness for young HPV-positive patients.[39-42] Moreover, from a societal perspective, the reduction in long-term radiation-induced complications is particularly relevant in working-age patients. Moreover, PT was reported to be cost-effective only for well selected patients,[43] hence assigning to MBS a crucial role. For example, in Chinese nasopharyngeal patients, a significant NTCP reduction (17%-

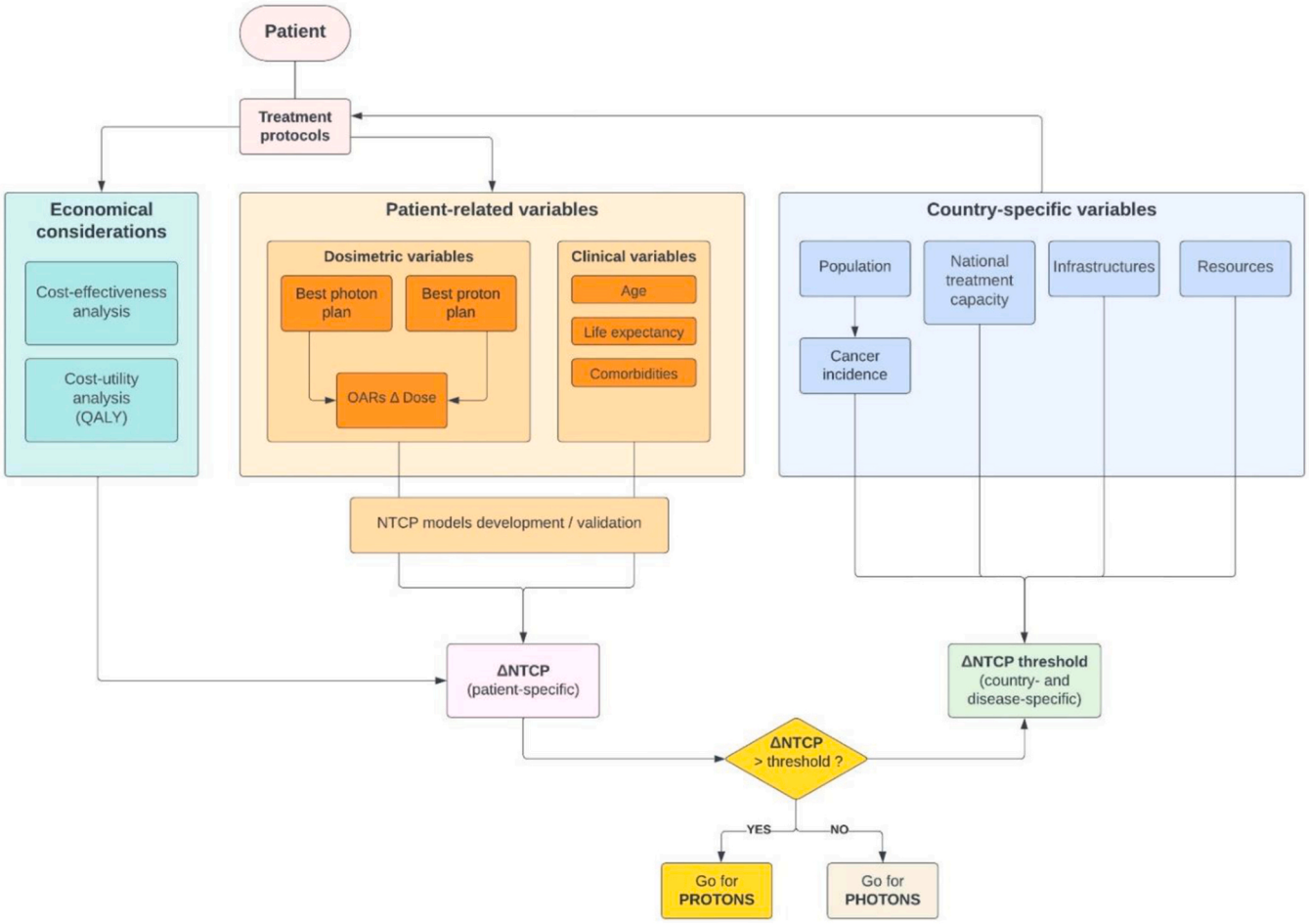

Figure 1. Schematic proposal of NTCP-based MBS in Italy and interplay between the variables involved.

39%, depending on patient's age) should be achieved to be considered cost-effective.[44] As well, in the Netherlands, IMPT for all HNCs did not prove cost-effectiveness over IMRT while the MBS did, with an estimated ICER of $80.170 and a societal willingness-to-pay (WTP) set to $106.400 (in 2010).[45] However, cost-effectiveness evaluations are strongly affected by the peculiarity of the health care system, the adopted perspective (health care sector versus societal perspective), and the ICER threshold, which expresses a country's WTP for health gains.[46] To date in Italy, there are no cost-effectiveness studies comparing PT with photon-RT, even though a WTP range of €25.000 to €40.000 was suggested.[47] Nonetheless, especially in northeastern Italy, a relevant increase in the HPV-positive HNCs was reported, which, together with population ageing, would encourage the adoption of an Italian MBS as a cost-effective tool.[48]

The Italian model-based selection scenario: Preliminary feasibility evaluations on the head and neck cancers proton therapy volumes

To date, three PT centers are in operation, all located in Northern Italy. The first Italian hadrontherapy facility was the National Center for Oncological Hadrontherapy (CNAO, Pavia), equipped with a synchrotron, which started clinical activity in 2011. It has three treatment rooms and plans for expansion, including a new proton gantry. The other two PT facilities in Trento at the *Azienda Provinciale per i Servizi Sanitari* (featuring two treatment rooms) and in Milan at the European Institute of Oncology (equipped with one treatment room) started clinical operations in October 2014 and in November 2023, respectively.[49] PT facility projects are ongoing in various regions. Therefore, with only three facilities in operation, it is evident that, besides the socio-economic point of view, PT accessibility may be strongly affected by a relatively reduced PT capacity. However, further PT centers are in the planning phase or under construction in Italy.[50]

In the following, we have estimated the optimal Italian HNC volume capacity. Under the hypothesis of a thirty-minute fraction time/HNC patient delivered in ten working hours/day, for a single-room facility, we assumed approximately 20 HNC treatment slots per day. On the other hand, two-room facilities still share the same proton beam while managing the in-room treatment preparation processes more efficiently. Hence, 35 overall treatment slots per day were assumed for a 2-room facility. In Italy the PT providers were considered as follows: one single-room facility (European Institute of Oncology) and two 2-room facilities (CNAO and Trento). Despite the three available treatment rooms, CNAO was regarded as a 2-room facility, considering the partial load ascribed to carbon ion RT. With respect to the HNC treatment load, we assumed a 7-week period to complete a full course of PT undergoing 35 treatment fractions delivered in 5 days/week. Under these assumptions, the Italian full HNC volume capacity was estimated in 643 HNC patients/year (Table 2). This estimation was made considering the highest number of potentially deliverable HNC slots that could be provided by the Italian PT centers, if they would be all dedicated only

Table 1
Comparative table for head and neck MBS relevant factors in Italy, Netherlands, and Denmark.

Country	Population (2021)	NHS	Economic and logistic support[31]	Patient selection	Main national RT/HN associations[32]	Total MV units (photon-RT) (2014)[33]	PT facilities in operation[a]
Italy	59 M	Italian Ministry of Health	PT Center only	LEA-based	AIRO, HEAD AND NECK WORKING GROUP	340	■ CNAO, Pavia ■ APSS Trento ■ IEO, Milano
The Netherlands	17.5 M	Dutch Health Council	PT Center and NHS	Model-based (NTCP)—in-silico planning comparison (ISPC)	NVRO, NVNBR,	132	■ UMCG PTC, Groningen ■ HollandPTC, Delft ■ ZON PTC, Maastricht
Denmark	5.8 M	Ministry of Health and Prevention	PT Center and NHS	Model-based (NTCP) preselection at local Oncology Department (6 DAHANCA Departments) followed by selection at PT center	DAHANCA	53	■ Dansk Center for Partikelterapi, Aarhus

Abbreviations: AIRO, Italian Association for Radiotherapy and Clinical Oncology (*Associazione Italiana di Radioterapia e Oncologia Clinica*); APSS, Trento PT facility (*Azienda Provinciale per i Servizi Sanitari*); CNAO, National Center for Oncological Hadrontherapy (*Centro Nazionale di Adroterapia Oncologica*); DAHANCA, The Danish Head and Neck Cancer Group; HN, head and neck; IEO, European Institute of Oncology (*Istituto Europeo di Oncologia*); ISPC, In-silico Planning Comparison; LEA, essential assistance levels (*Livelli Essenziali di Assistenza*); M, million; MV, megavolt (ie, photon-RT); NHS, National Health System; NTCP, normal tissue complication probability; NVMBR, Dutch Society of Medical Imaging and Radiotherapy; NVRO, Dutch Society for Radiotherapy and Oncology; PT, proton therapy; PTC, PT center; RT, radiation therapy; UMCG, University Medical Center Groningen (*Universitair Medisch Centrum Groningen*).

[a] PT centers in which HNC is not treated are not included in the table (eg, INFN-LNS, Catania, Italy).[25]

to HNCs. However, it is worth noticing that the applied fraction time and fractionation scheme could be extended to other PT malignancies or balance treatment workloads with different time-consumption (eg, the use of hypofractionated schemes when indicated). With this consideration, a reasonably similar Italian PT volume could be envisioned even when accounting for a realistic and heterogeneous treatment workload.

Tambas et al.[20] published the first Dutch experience in 2020, reporting the cancer-site-based proportion of patients selected for PT according to the NIPP-HNC, in Groningen Proton Therapy Center. Moreover, a Dutch PT report was published in 2022 to report the number of HNC treated with PT.[51] Due to the unavailability of relevant clinical variables, a propensity score matching with the Italian HNC population was not possible. Furthermore, NIPP-HNC, in the Tambas publication, evaluated only HNC originating from oral cavity, larynx, and pharynx was selected for definitive RT, hence resulting in a further critical reduction of the sample. To roughly investigate the HNC PT Italian volumes per year, we based our analysis on the incidence per cancer site derived from 2022 Global Cancer Observatory (GCO, 2022).[52,53] Naïve scaling factors were computed on population and incidence per cancer site basis in order to adjust the Dutch results to the Italian scenario. Hence, we reported Tambas single-center proportions to a national level with the aid of the Dutch PT report.[51] Finally, we applied the Dutch proportions to derive the corresponding HNCs selected for PT in a hypothetical Italian landscape.[34] In this framework, with respect to the presented naïve analysis, the PT facility workload derived from HNC MBS exceeds the overall current PT Italian capacity with 810 estimated patients/year (ie, 125.9%). All the assumptions and data used to estimate the Italian MBS HNC PT volumes were summarized in Table 3.

Discussion

In the Italian scenario, challenges and opportunities underlay the implementation of an HNC MBS for PT. We suggested the establishment of an efficient PT HNC network, with widespread territorial dissemination, as the Italian MBS core. Such a collaborative group, supported by the international PT community, would serve firstly to define the MBS protocol to be approved by the Italian NHS and afterward to actively implement the MBS processes while diffusing the concept of PT as a nationally shared and valuable oncological treatment resource. A centralized approach to MBS is warranted in order to perform uniform NTCP analysis and efficiently administer IT dedicated resources, while supporting local photon-RT facilities. From a technical perspective, the need for a centralized EMR was also highlighted as essential to provide the needed structured data to feed the MBS NTCP models and the optimal Italian ΔNTCP value. However, although the Italian routine usage of EMR has increased significantly in the past few years, the achievement of acceptable compliance at the Italian national scale is still distant, hence representing one of the biggest challenges. Regarding EMR, with the recent ProTRAIT (PROton Therapy ReseArch RegIsTry[54]) initiative, the Netherlands provided valuable insights on tumor data standardization. Furthermore, dedicated scientific network, including the European SocieTy for Radiotherapy and Oncology European Particle Therapy Network, were recently designed to gather PT evidence.[55-57] Also, in this regard, Italian national clinical registries and efficient IT infrastructure (eg, 5G communication technologies, fiber optic networks, cryptographic sciences) would provide a valuable contribution. Moreover, it would be of great importance also from a financial perspective, as the lack of evidence on the effective value of PT over photon-RT impacts the establishment of PT national reimbursement policies especially in countries with a public health care prevalence, such as in Europe. Literature studies reported PT as cost-effective treatment only for young patients with a longer life expectation[39,58,59] and patients with better prognosis due to biological tumor traits[60-62] that would achieve a relevant reduction in long-term

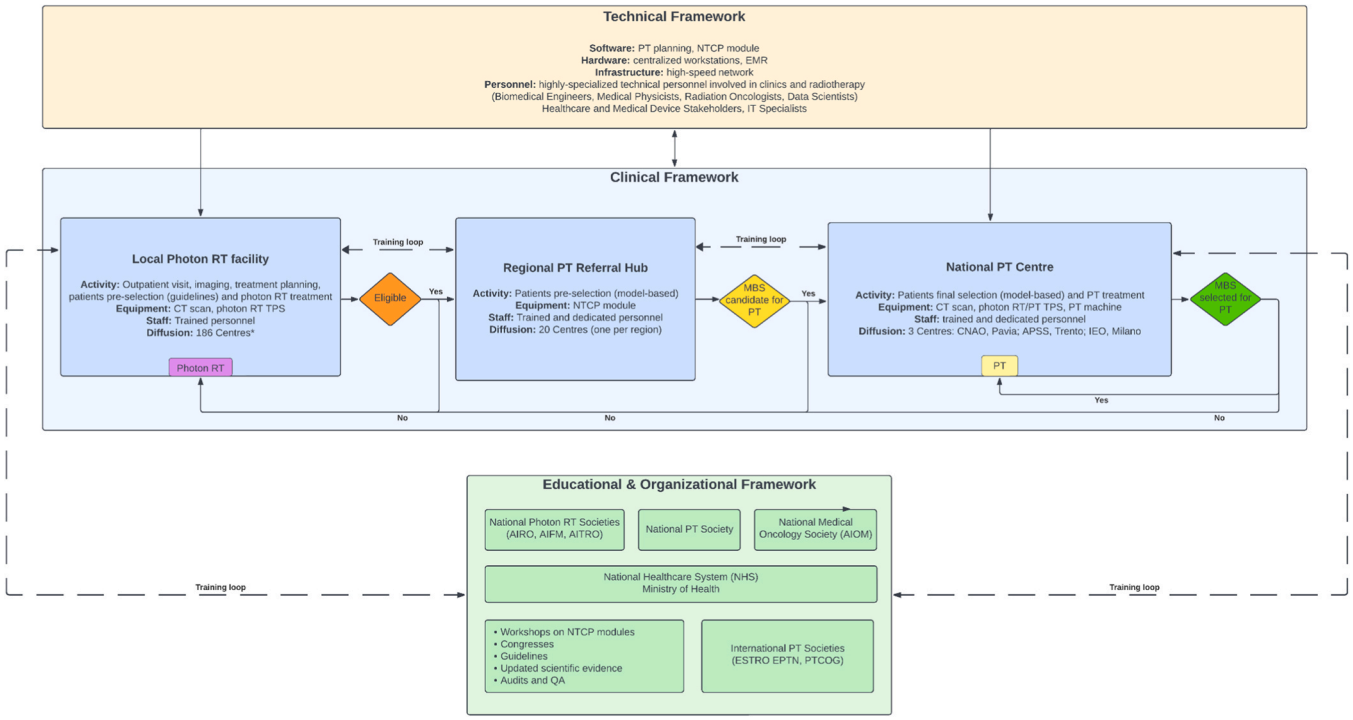

Figure 2. Envisioned Italian model-based selecting proton therapy for HNC patients: key factors and pipeline. *Abruzzo (2), Basilicata (2), Calabria (4), Campania (18), Emilia-Romagna (12), Friuli Venezia Giulia (3), Lazio (19), Liguria (5), Lombardia (35), Marche (4), Molise (1), Piemonte (14), Puglia (11), Sardegna (4), Sicilia (18), Toscana (15), Trentino Alto Adige (3), Umbria (5), Valle D'Aosta (1), Veneto (10).[36] Abbreviations: AIFM, Italian Association of Medical Physics; AIOM, Italian Association of Medical Oncology; AIPT, Italian Association for Particle Therapy (*hypothetic acronym*); AIRO, Italian Association of Radiotherapy and Clinical Oncology; AITRO, Italian Association of Radiation Therapists and Physicist Technicians; CT, computed tomography; EMR, electronic medical record; IT, information technology; MBS, model-based selection; NHS, National Health System; NTCP, normal tissue complication probability; PT, proton RT; QA, quality assurance; RT, radiation therapy; TPS, Treatment Planning System.

Table 2
Underlying assumptions for the Italian proton therapy capacity, in the context of HNC full-course proton treatment.

Italian MBS: assumptions and workload

	Two-room facility	Single-room facility	Italian PT
Treatment slot/day	35	20	90
weeks/HNCs PT	7	7	7
working weeks/year	50	50	50
working hours/day	10	10	10
# facilities	2	1	3
HNCs PT slot/year	500	143	643

morbidity.[63,64] In the described scenario, the treatment of radiation-induced toxicities may lead to important health care and social costs,[42] making MBS cost-effective, as reported in the Netherlands.[45] In the Italian landscape, efforts should be also made toward more efficient and sustainable PT reimbursement processes as well as socio-economic patient support (eg, prevention, traveling, and accommodation). In the context of PT, geographical disparities were reported both in the US and Europe,[31] due to PT-related costs (eg, long-distance traveling, accommodation). In Italy, such territorial disparities may be even sharpened due to the imbalanced geographical distribution of PT facilities. Furthermore, such circumstances guided our suggestion toward a centralized Italian MBS, although the workload on the dedicated team should be monitored and minimized. Recently, automated NTCP methods for candidates' preselection were suggested in literature, ranging from organs at risks overlap-based[37,65] to deep learning augmented modeling.[38] In the near future, such tools are expected to significantly reduce time and efforts required from the MBS dedicated team as well as the needed IT resources. Finally, we attempted to perform a preliminary estimation of the Italian MBS PT workload. Based on the data available on GCO and the reported number of inhabitants in 2020, we reported the NIPP-HNC Dutch candidates to the Italian scale. A 125.9% PT facility workload was estimated. In consideration of the actual operating Italian PT facilities, such workload is over our capacity. This leads to considerations about the opportunity to select specific clinical scenarios based on age, site, and stage or to increase the delta NTCP to qualify patients for protons. Approaches like hypofractionation, although not clinically established in HNC PT,[66] or combined photon-proton treatment,[67] may also reduce the impact of such therapy on the overall PT workload. However, our analysis presents some important limitations, including the fact that the GCO Italian report is not comprehensive, with only the main available regional registries providing cancer information, and no clinical variables were included in the analysis. A propensity score matching would have been appropriate to match the NIPP-HNC Dutch candidates to the corresponding Italian HNC sample. Nevertheless, a certain amount of approximation would still underlay the HNC PT volume estimation due to matching method limitations and the unavailability of potentially relevant unknown and known clinical data (eg, HPV status). Finally, it is worth mentioning that the MBS infrastructure, herein proposed for

Table 3
Italian volume estimations on a national scale, derived from model-based PT selection approach in HNC (single-center experience), combined with the HNC data from the Dutch PT report published in 2022.

			Single-center experience				National scale estimates
			All radiation therapy kinds		Protons		Protons
HN cancer type	Country	Incidence (Globocan 2022)	20 mo (Tambas, NL)	12 months	20 mo (Tambas, NL)	12 mo	12 mo
Lip, oral cavity	NL	*1568*	*7*	4	*5*	3	12
	IT	*4881*					38
Larynx	NL	*660*	*66*	40	*8*	5	20
	IT	*4275*					128
Oropharynx	NL	*432*	*79*	47	*51*	31	126
	IT	*1532*					445
Hypopharynx	NL	*227*	*10*	6	*6*	4	15
	IT	*591*					38
Nasopharynx	NL	*82*	*10*	6	*10*	6	25
	IT	*532*					160
Tot HN	NL	2969	172	103	80	48	*197*
	IT	11,811					810

Data from literature are in italic.

HNCs, may be extended to other categories of patients potentially eligible for PT, and that PT technologies availability in Italy will increase in the future.[50]

Moreover, despite being an innovative solution for accurate patients' selection, NTCP models suffer from inherent limitations that should be carefully considered. First of all, NTPC models used in Denmark and the Netherlands are validated for Danish and Dutch population, respectively, but not for the Italian one. Secondly, from a clinical point of view, the additional time necessary for planning and NTCP analysis might cause treatment delays and compromise outcomes. From an organizational standpoint, such additional workload for the staff and the need for training of all involved clinical professionals should be also considered. Finally, technical impediments due to north-south digital divide in Italy and strict regulatory policies when sharing data might represent an additional obstacle to the real-world implementation of such infrastructure.

Conclusion

In conclusion, we strongly suggest the implementation of a centralized Italian NTCP model-based selection approach for HNC PT. The envisioned Italian MBS would be led by a dedicated expert team operating within a novel Italian PT framework. The estimated workload for HNC patient potentially eligible for PT is not compatible with the current treatment capacity of the PT centers operating in Italy at their best organizational level. However, with respect to the current scenario, and the future advances both in terms of technology and new PT facilities, an adjusted MBS may represent a feasible, sustainable, and cost-effective opportunity for HNC patients to be selected for the best treatment option.

Ethics

Not applicable.

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No funding was received for conducting this study.

Author Contributions

Ester Orlandi: Conceptualization, Resources, Supervision. Ester Orlandi, Giulia Fontana, Matteo Pepa: Methodology, Project administration. Ester Orlandi, Matteo Pepa, and Giulia Fontana: Writing-original draft preparation. All authors: Writing- review and editing. Matteo Pepa and Giulia Fontana: Visualization. NA: Software, Validation, Formal analysis, Investigation, Data curation, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declaration of Conflicts of Interest

Ester Orlandi, MD, is an Associate Editor of the International Journal of Particle Therapy. The authors declare no additional conflicts of interest.

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