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Carbon-Ion Radiotherapy for Oral Non-Squamous Cell Carcinoma: Clinical and Radiophysical Perspectives for Indonesia

Ringgit Purbowati, and Raditya Faradina*

Department of Physics, Faculty of Mathematic and Natural Sciences, Defense University, IPSC Sentul Bogor, Indonesia, 16810

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Abstract

Oral non-squamous cell carcinoma (non-SCC) represents a radioresistant malignancy that often responds poorly to conventional X-ray radiotherapy. This resistance creates major clinical challenges, especially in resource-limited settings such as Indonesia. Carbon-ion radiotherapy (C-ion RT) has emerged as an advanced treatment modality that offers superior dose distribution and higher biological effectiveness, making it particularly promising for tumors that are refractory to photon therapy. A systematic narrative review was conducted following the PRISMA 2020 framework. Literature searches in PubMed, Scopus, and ScienceDirect (January 2013–June 2024) used the terms "carbon-ion radiotherapy," "oral cancer," "non-squamous cell carcinoma," "clinical outcome," and "toxicity." Studies reporting quantitative data on treatment outcomes were included and analyzed descriptively from both clinical and medical physics perspectives. Thirty-two eligible studies were reviewed, including data from Japan, Germany, and Italy. Across these cohorts C-ion RT achieved a mean 5-year local control rate of 78.8% and an overall survival rate of 58.3%, outperforming conventional X-ray radiotherapy and demonstrating superiority over proton therapy in biological effectiveness (RBE ≈ 2–3). The dominant acute toxicity was mild-to-moderate oral mucositis (≈28%, grade 1–2), while late osteoradionecrosis occurred in 10–14% of cases but was largely manageable with conservative care. C-ion RT offers a unique combination of physical precision and biological potency that makes it highly effective for radioresistant oral cancers. For Indonesia, its gradual implementation—supported by international collaboration, workforce training, and national policy integration—could enhance cancer treatment capacity and stimulate innovation in medical physics and radiotherapy technology. This review also discusses the strategic readiness for integrating C-ion RT into Indonesia's healthcare system.

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Abstrak

Karsinoma non-sel skuamosa rongga mulut (non-SCC) merupakan jenis keganasan yang bersifat radioresisten dan sering menunjukkan respons yang kurang optimal terhadap radioterapi sinar-X konvensional. Resistensi ini menimbulkan tantangan klinis yang signifikan, khususnya di negara dengan keterbatasan sumber daya seperti Indonesia. Terapi radiasi ion karbon (Carbon-ion Radiotherapy, C-ion RT) telah muncul sebagai modalitas pengobatan lanjut yang menawarkan distribusi dosis yang lebih unggul serta efektivitas biologis yang lebih tinggi, sehingga sangat menjanjikan untuk tumor yang refrakter terhadap terapi foton. Sebuah tinjauan naratif sistematis dilakukan berdasarkan kerangka PRISMA 2020. Pencarian literatur pada database PubMed, Scopus, dan ScienceDirect (Januari 2013–Juni 2024) menggunakan kata kunci "carbon-ion radiotherapy," "oral cancer," "non-squamous cell carcinoma," "clinical outcome," dan "toxicity." Studi yang melaporkan data kuantitatif terkait luaran terapi disertakan dan dianalisis secara deskriptif dari sudut pandang klinis dan fisika medis. Sebanyak tiga puluh dua studi memenuhi kriteria inklusi, mencakup data dari Jepang, Jerman, dan Italia. Secara keseluruhan, C-ion RT menghasilkan rerata angka kontrol lokal 5 tahun sebesar 78,8% dan angka keselamatan hidup

* Corresponding author.
E-mail address: radityafaradina@gmail.com

5 tahun sebesar 58,3%, melampaui hasil radioterapi sinar-X konvensional serta menunjukkan superioritas dibandingkan terapi proton dalam efektivitas biologis (RBE ≈ 2–3). Toksisitas akut yang paling sering ditemukan adalah mukositis oral derajat ringan hingga sedang (≈28%, derajat 1–2), sedangkan osteoradionekrosis tardif terjadi pada 10–14% kasus namun umumnya masih dapat ditangani dengan terapi konservatif. C-ion RT menawarkan kombinasi unik antara presisi fisik dan potensi biologis yang menjadikannya sangat efektif untuk kanker rongga mulut yang bersifat radioresisten. Bagi Indonesia, implementasi bertahap yang didukung kolaborasi internasional, pelatihan tenaga profesional, serta integrasi kebijakan nasional berpotensi meningkatkan kapasitas layanan kanker sekaligus mendorong inovasi di bidang fisika medis dan teknologi radioterapi. Tinjauan ini juga membahas kesiapan strategis Indonesia dalam mengintegrasikan C-ion RT ke dalam sistem pelayanan kesehatan nasional.

1. Introduction

Cancer remains a major public health problem in Indonesia. According to GLOBOCAN 2022 data, Indonesia recorded 408,661 new cancer cases and 242,099 cancer-related deaths (International Agency for Research on Cancer [IARC], 2023), with mortality largely attributed to delayed diagnosis and limited access to radiotherapy (Kementerian Kesehatan Republik Indonesia [Kemenkes RI], 2022). Among head and neck malignancies, non-squamous cell carcinoma (non-SCC) constitutes around 6–10% of all oral cancers. Although relatively rare, its radioresistant nature makes it one of the most difficult oral cancers to treat using conventional radiotherapy (Ikawa et al., 2019). If left inadequately treated, oral non-SCC can lead to impaired vital functions such as speech, mastication, and swallowing, thereby significantly reducing patients' quality of life (Cleary et al., 2017).

Over the past two decades, carbon-ion radiotherapy (C-ion RT) has emerged as an advanced particle-beam modality offering both physical and biological advantages for managing radioresistant tumors (Durante & Loeffler, 2010; Kamada et al., 2018). Physically, carbon ions possess a high mass and double charge, resulting in a high Linear Energy Transfer (LET) that produces dense energy deposition along the ion track and creates a sharp Bragg peak. This characteristic allows the maximum dose to be concentrated precisely within the tumor volume while sparing adjacent healthy tissues (Tsujii & Kamada, 2012; Kanai et al., 2011; Kase et al., 2006). Biologically, the dense ionization pattern enhances the Relative Biological Effectiveness (RBE) of carbon ions, reflecting their capacity to induce complex, irreparable DNA double-strand breaks in cancer cells (Kase et al., 2006; Friedrich et al., 2013). The combination of these physical and biological advantages allows C-ion RT to deliver higher effective doses with minimal collateral damage. Compared with photons or protons, carbon ions demonstrate distinct depth-dose characteristics—higher LET and superior dose conformity—which constitute the physical foundation of their clinical efficacy.

Clinical evidence consistently supports this potential. Studies from Japan, Germany, and Italy have demonstrated that C-ion RT achieves higher tumor control and survival rates in non-SCC head and neck cancers, including salivary gland carcinoma and mucosal melanoma (Hayashi et al., 2021; Jensen et al., 2020). For instance, Ikawa et al. (2019) reported a five-year local control rate of 78.8% and an overall survival rate of 58.3% in patients with oral non-SCC, with manageable complications such as osteoradionecrosis. The long-term experience of facilities in Japan, Germany, and Italy further indicates that C-ion RT can become an integral part of modern cancer care when supported by adequate infrastructure and regulatory frameworks (Durante & Loeffler, 2010; Kamada et al., 2018). Japan's National Institute of Radiological Sciences (NIRS) has led this innovation since 1994, establishing a strong clinical record and serving as a technological model for international adoption (Kamada et al., 2018; Tsujii & Kamada, 2012).

In contrast, Indonesia faces structural challenges. With only around 75 linear accelerator (linac) units serving a population of more than 270 million, the country remains far below the World Health Organization (WHO) recommendation of one linac per 250,000 people (International Atomic Energy Agency [IAEA], 2023; World Health Organization [WHO], 2022). The shortage of trained medical physicists, uneven geographic distribution of facilities, and high infrastructure costs of particle-therapy accelerators make the introduction of advanced modalities such as C-ion RT particularly challenging. Nevertheless, integration of particle-therapy technology could represent a transformative step toward improving national cancer control, strengthening domestic research in medical physics, and enhancing national healthcare resilience (Vanderstraeten et al., 2022; Beltran & Snyder, 2018).

Despite growing international evidence supporting carbon-ion radiotherapy, no comprehensive review has yet integrated its clinical outcomes with radiophysical and radiobiological perspectives—particularly within the context of Indonesia's healthcare system. This gap highlights the need for a holistic synthesis that not only evaluates clinical performance but also connects it to the fundamental physical and biological principles that make C-ion RT uniquely effective for radioresistant oral cancers. Bridging these domains provides a necessary framework for assessing both the scientific rationale and practical feasibility of introducing particle-therapy technology in Indonesia.

Therefore, this review aims to synthesize recent clinical and physical evidence on the efficacy of carbon-ion radiotherapy for oral non-SCC, emphasizing its radiobiological mechanisms, dose-response characteristics, and clinical outcomes. Furthermore, it explores the strategic challenges and future perspectives for implementing particle-therapy technology in Indonesia from a medical-physics standpoint.

2. Research Methods

This study employed a systematic narrative review design, structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines (Page et al., 2021). The review aimed to synthesize the most recent evidence on the clinical effectiveness and safety of carbon-ion radiotherapy (C-ion RT) for oral non-squamous cell carcinoma (non-SCC), while also exploring its potential implementation in Indonesia from a medical-physics perspective.

A comprehensive literature search was performed in PubMed, Scopus, and ScienceDirect databases for studies published between January 2013 and June 2024. The following combination of keywords and Boolean operators was used: "carbon-ion radiotherapy" AND ("oral cancer" OR "head and neck cancer") AND "non-squamous cell carcinoma" AND ("clinical outcome" OR "toxicity"). Articles that met the inclusion criteria comprised prospective or retrospective studies presenting quantitative data on local control (LC), overall survival (OS), progression-free survival (PFS), and radiation-related toxicities in patients with non-SCC cancer. Articles in the form of reviews, editorials, conference abstracts, animal studies, or those irrelevant to the topic were excluded from the analysis. From a total of 102 identified records, 32 studies met the inclusion criteria after thorough screening of titles, abstracts, and full-text articles.

Data extracted from each study included patient characteristics, C-ion RT dose and fractionation schedules, clinical outcomes, and toxicity profiles. Particular attention was given to studies reporting dosimetric or physical parameters, such as dose–volume indices, Linear Energy Transfer (LET) distributions, and Relative Biological Effectiveness (RBE)-weighted doses expressed in Gy(RBE). This approach aimed to provide a comprehensive understanding from both clinical and medical-physics perspectives.

Given the variations in study design and treatment regimens, the results were summarized narratively to identify general trends in treatment efficacy and safety. All data were obtained from publicly accessible sources; therefore, no ethical approval was required for this review.

3. Results and Discussions

3.1 Physical and Radiobiological Basis of Carbon-Ion Radiotherapy (C-ion RT)

The fundamental advantage of carbon-ion radiotherapy (C-ion RT) lies in its superior physical and radiobiological characteristics compared to conventional photon or proton therapy. Carbon ions have greater mass and a double positive charge, resulting in reduced lateral scattering and a sharply defined Bragg peak, which allows highly localized energy deposition within the tumor volume while minimizing exposure to surrounding normal tissues. This precise depth–dose distribution contributes to better conformity in complex head and neck tumor geometries. The sharp dose fall-off enables the delivery of a higher ablative dose in fewer fractions (hypofractionation) without exceeding the tolerance limits of adjacent critical organs.

From a radiobiological standpoint, carbon ions exhibit a high Linear Energy Transfer (LET) of approximately 50–100 keV/µm, leading to dense ionization clusters and complex DNA double-strand breaks that are difficult for cancer cells to repair. Consequently, the Relative Biological Effectiveness (RBE) of carbon ions is around 2–3, approximately twice that of photons, enabling superior tumor cell killing, especially in hypoxic or radioresistant tumors such as oral non-squamous cell carcinoma (non-SCC).

These combined physical and biological properties form the scientific foundation for the observed clinical advantages of C-ion RT. The following section summarizes current clinical outcomes from studies involving patients with oral non-SCC treated using this modality.

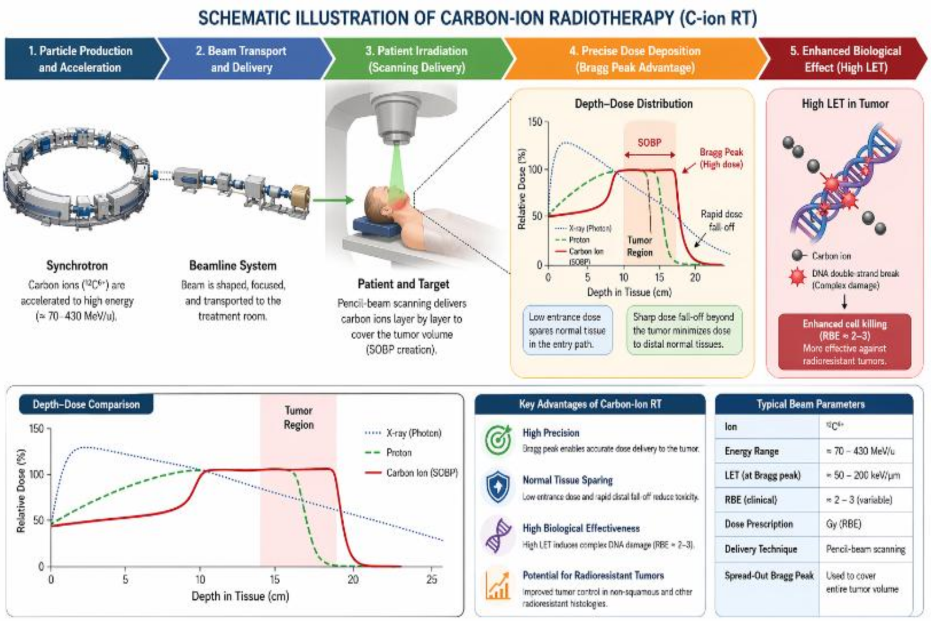

Figure 1. Schematic illustration of carbon-ion radiotherapy (C-ion RT). Carbon ions are accelerated in a synchrotron and delivered through a beamline system to the patient. The depth–dose profile shows a low entrance dose followed by a sharp Bragg peak at the tumor site, forming a Spread-Out Bragg Peak (SOBP) to cover the tumor volume. The high Linear Energy Transfer (LET) at the Bragg peak enhances biological effectiveness (RBE ≈ 2–3), resulting in efficient tumor cell killing while sparing surrounding healthy tissues.

To further illustrate the working principle of carbon ion radiotherapy, a schematic representation is provided in **Figure 1**. In C-ion RT, carbion ions are accelerated using a synchrotron and directed toward the patient through a beam delivery system. As the ions penetrate tissue, they deposit a relatively low dose along the entry path, followed by a sharp increase in energy deposition at the tumor site, known as the Bragg Peak. Beyond this peak, the dose rapidly falls to near zero, minimizing exposure to surrounding healthy tissues.

This precise dose localization is further enhanced by active beam scanning technique, which allow the formation of a Spread-Out Bragg Peak (SOBP) to cover the entire tumor volume. Simultaneously, the high Linear Energy Transfer (LET) of carbon ions induces complex DNA double-strand breaks, leading to enhanced tumor cek killing compared to photons or protons.

3.2 Clinical Outcomes of Carbon-Ion Radiotherapy for Oral Non-SCC

From the thirty-two studies analyzed, most were conducted in Japan, Germany, and Italy—countries that currently operate clinical carbon-ion radiotherapy centers. Overall, C-ion RT provided superior local control and survival outcomes compared with conventional photon or proton therapy. Across these studies, a five-year local control (LC) rate of 78.8% and an overall survival (OS) rate of 58.3% were reported for patients with oral non-SCC treated using carbon-ion radiotherapy (Ikawa et al., 2019). These findings indicate a clear advantage compared with conventional photon-based radiotherapy (X-ray), which typically achieves only 40–50% local control in radioresistant head and neck cancers and is often associated with high recurrence rates. When compared with proton therapy, C-ion RT demonstrated superior biological effectiveness, primarily due to its higher Relative Biological Effectiveness (RBE ≈ 2–3). Although protons possess a physical advantage in dose distribution through the Bragg peak phenomenon, their biological effectiveness remains close to that of photons (RBE ≈ 1). In contrast, carbon ions exhibit substantially higher RBE values (approximately 2–3), resulting in more complex and irreparable DNA damage in radioresistant tumors (Kase et al., 2006; Friedrich et al., 2013).

Despite its superior clinical effectiveness, C-ion RT also presents challenges related to soft- and hard-tissue toxicity. The most frequently reported complication is osteoradionecrosis (ORN), with an incidence of approximately 13.5%, slightly higher than that reported for proton therapy, which typically remains below 10% (Ikawa et al., 2019; Ohnishi et al., 2020; Koto et al., 2017). The risk of ORN increases in tumors located adjacent to the mandibular bone and in cases where high doses (>60 Gy[RBE]) are delivered to dense bony structures (Koto et al., 2017; Shirai et al., 2022). Nevertheless, most patients are able to maintain essential functions such as eating and swallowing through appropriate medical management.

Overall, the toxicity profile of C-ion RT remains within clinically acceptable tolerance limits, with most adverse effects manageable through supportive care or conservative interventions (**Figure 2**). Compared with X-ray and proton therapy, C-ion RT offers a favorable balance between improved tumor control and manageable toxicity. This superior biological effectiveness makes it one of the most promising treatment modalities for oral non-SCC cancers that are difficult to manage using conventional radiotherapy (Hayashi et al., 2021; Jensen et al., 2020).

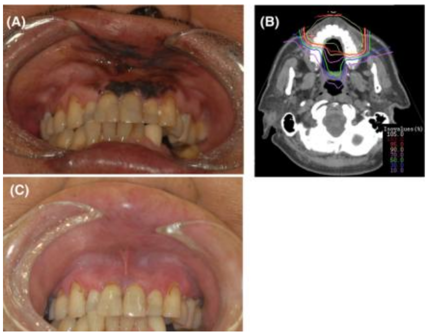

Figure 2. Case of mucosal melanoma of the upper gingiva in a 64-year-old male with invasion into the maxillary bone. The patient refused radical surgery and underwent carbon-ion radiotherapy (C-ion RT) with a total dose of 57.6 Gy (RBE) delivered in 16 fractions. Twenty months after treatment, evaluation showed complete tumor disappearance without severe complications, including osteoradionecrosis of grade ≥2

Overall, clinical outcomes demonstrated that C-ion RT provides high tumor control (LC) in head and neck non-SCC cancers, with an average five-year rate of 78–80% (Ikawa et al., 2019; Koto et al., 2017). The five-year overall survival (OS) ranged between 58–66%, which is considered favorable given that most patients presented with advanced disease or refused surgical intervention (**Table 1**). Conversely, the progression-free survival (PFS) remained limited to around 36%, indicating that distant metastasis continues to be a major determinant of long-term prognosis. These findings reinforce that C-ion RT is highly effective in controlling the primary oral cavity tumors through its high RBE mechanism. However, to address the limited PFS and improve patients' overall survival, future clinical protocols in Indonesia must prioritize the integration of C-ion RT with advanced systemic therapies, such as molecular-targeted agents or checkpoint immunotherapy, to manage micrometastasis.

Table 1. Summary of main clinical results of carbon-ion radiotherapy (C-ion RT) for oral non-squamous cell carcinoma (non-SCC)*

Study	*Country*	*Dose (Gy[RBE])*	*LC (%)*	*OS (%)*	*Major Toxicity*
Ikawa et al., 2019	Japan	64.0/16 fx	78.8	58.3	ORN 13%
Hayashi et al., 2021	Japan	57.6/16 fx	81.6	61.2	Mucositis 25%
Jensen et al., 2020	Germany	60.0/15 fx	76.0	63.0	Xerostomia 12%
Matsunobu et al., 2012	Japan	64.0/16 fx	80.0	66.0	ORN 10%

LC: local control; OS: overall survival; ORN: osteoradionecrosi

** Source: adapted from Ikawa et al. (2019), Hayashi et al. (2021), Jensen et al. (2020), and Matsunobu et al. (2012)*

3.3 Adverse Effect of Carbon-Ion Radiotherapy

Although carbon-ion radiotherapy (C-ion RT) provides excellent local control and survival outcomes, treatment-related toxicities remain an important clinical consideration. Across most studies, adverse effects were generally mild to moderate and could be managed within standard supportive care. The most common acute toxicity was oral mucositis, observed in approximately 25–30% of patients, typically of Grade 1–2 severity (**Table 2**).

Severe mucositis (Grade ≥3) occurred in less than 3% of cases and was usually controlled with topical rinses, analgesics, and oral hygiene support (Ikawa et al., 2019). Radiation dermatitis was also reported in approximately 15–20% of patients, presenting mainly as transient erythema or desquamation that resolved with topical treatments.

Among late toxicities, osteoradionecrosis (ORN) of the jaw represented the most clinically significant complication, with an incidence ranging from 10% to 14% (Koto et al., 2017; Tsujii, 2012). Most ORN cases were mild (Grade 1–2) and successfully managed conservatively using antibiotics, dental care, or hyperbaric oxygen therapy. Other chronic effects, including xerostomia, taste alteration, and trismus, were less common and generally reversible.

These findings confirm that, despite the high Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE) of carbon ions, C-ion RT maintains a favorable therapeutic ratio by achieving high tumor control while keeping toxicity within acceptable clinical limits. Proper dose optimization and jawbone protection during treatment planning are essential to minimize the risk of late complications such as ORN (Shirai et al., 2022).

Table 2. Summary of Major Adverse Effects Reported in C-ion RT for Oral Non-SCC*

Type of Adverse Effect	Typical Incidence	Severity	Clinical Notes	Source
Oral mucositis (acute)	25–30%	Mostly Grade 1–2	Resolves with supportive oral care	Ikawa et al., 2019
Radiation dermatitis (acute)	15–20%	Grade 1–2	Transient erythema; heals with topical therapy	Tsujii, 2012
Osteoradionecrosis (late)	10–14%	Mostly mild	Managed with antibiotics or hyperbaric oxygen	Koto et al., 2017
Xerostomia / Trismus (late)	<10%	Mild	Usually reversible	Ikawa et al., 2019

** Source: adapted from Ikawa et al. (2019), Koto et al. (2017), and Tsujii (2012).*

3.4. Implication for Indonesia

The implementation of carbon-ion radiotherapy (C-ion RT) in Indonesia carries significant implications for both national cancer control and the advancement of medical-physics research.

Currently, Indonesia operates approximately 75 linear accelerator (linac) units to serve more than 270 million people, far below the World Health Organization (WHO) recommendation of one unit per 250,000 population (International Atomic Energy Agency [IAEA], 2023; World Health Organization [WHO], 2022). This disparity highlights the urgent need to expand national radiotherapy infrastructure, strengthen human-resource capacity, and enhance technological readiness before adopting particle-therapy systems such as carbon-ion accelerators.

From a technical perspective, a C-ion RT facility requires major investment in accelerator infrastructure, beam-delivery systems, and radiation-shielding design. The core technology typically consists of a synchrotron or synchro-cyclotron accelerator capable of accelerating carbon ions up to 290–430 MeV/u, enabling therapeutic penetration depths of approximately 25–30 cm in tissue (Tsujii & Kamada, 2012; Kanai et al., 2011; Tsujii, 2012). A complete facility also includes a beam-transport line, a scanning and dose-modulation system, and a treatment-planning system (TPS) that performs LET-based biological optimization and RBE-weighted dose calculations—areas in which medical physicists play a central role. Shielding and radiation-safety design must comply with the IAEA Safety Standards Series SSG-46 and regulations issued by the Indonesian Nuclear Energy Regulatory Agency (BAPETEN) (International Atomic Energy Agency [IAEA], 2018; Badan Pengawas Tenaga Nuklir [BAPETEN], 2013).

Beyond hardware readiness, human-resource development is equally crucial. Indonesia faces a shortage of certified medical physicists, radiotherapy engineers, and dosimetrists capable of operating and maintaining high-energy particle systems (International Organization for Medical Physics [IOMP], 2021). Structured academic programs and international collaboration with leading centers such as the National Institute of Radiological Sciences (NIRS) in Japan, the Heidelberg Ion-Beam Therapy Center (HIT) in Germany, and the National Center for Oncological Hadrontherapy (CNAO) in Italy would be essential (National Institute of Radiological Sciences [NIRS], 2021; Heidelberg Ion-Beam Therapy Center [HIT], 2023; National Center for Oncological Hadrontherapy [CNAO], 2022). Such partnerships could take the form of joint research projects, staff exchanges, and beam-modeling workshops under the coordination of the National Research and Innovation Agency (BRIN) and the Ministry of Health (Kemenkes RI).

From a policy standpoint, the development of particle therapy should align with Indonesia's National Cancer Control Action Plan (RAN-P 2020–2025) and the National Research Priority Agenda focusing on health resilience and advanced radiation technology (Kementerian Kesehatan Republik Indonesia [Kemenkes RI], 2020; Badan Riset dan Inovasi Nasional [BRIN], 2024). A phased national roadmap is therefore recommended (**Table 3**), combining feasibility studies, capacity building, and progressive infrastructure development under unified inter-agency coordination.

Table 3. Proposed Strategic Phases for Carbon-Ion Radiotherapy Implementation in Indonesia*

Phase	*Focus Area*	*Main Activities*	*Key Stakeholders*
Phase 1	Feasibility & Policy Framework	Technical–economic assessment, stakeholder mapping, cost–benefit analysis	BRIN, Kemenkes, BAPETEN
Phase 2	Capacity Building & Training	National curriculum; staff training abroad (NIRS, HIT, CNAO)	Universities, Hospitals, IOMP
Phase 3	Infrastructure Development	Design & construction of pilot C-ion RT center; regulatory licensing	BRIN, BATAN legacy, BAPETEN
Phase 4	Clinical Integration & Research	Commissioning, multicenter trials, inclusion in national cancer program	Kemenkes, Hospitals, Academic Network

*Source: adapted from WHO, IAEA, BRIN, 2024

The establishment of a pilot C-ion RT center would not only expand Indonesia's clinical capability but also stimulate domestic innovation in accelerator physics, dosimetry instrumentation, and computational modeling. Such integration could ultimately position Indonesia as a regional hub for particle-therapy research and education, reinforcing both national health security and scientific independence.

4. Conclusions

This review confirms that carbon-ion radiotherapy (C-ion RT) provides significant clinical and radiobiological advantages in the management of oral non-squamous cell carcinoma (non-SCC). Across multiple studies, C-ion RT consistently demonstrates superior local control and overall survival compared with conventional photon therapy, while maintaining acceptable levels of toxicity. Quantitatively, the analyzed studies report a mean 5-year local control (LC) rate of approximately 78–80% and an overall survival (OS) rate of 58–66%, which are markedly higher than those achieved with conventional photon radiotherapy (LC ≈ 40–50%). The incidence of acute toxicities, particularly oral mucositis, remains around 25–30% (predominantly Grade 1–2), while late toxicities such as osteoradionecrosis occur in approximately 10–14% of cases and are generally manageable with conservative treatment.

These findings indicate that C-ion RT achieves a favorable therapeutic ratio, combining high tumor control probability with acceptable toxicity levels. Its unique combination of high Linear Energy Transfer (LET), enhanced Relative Biological Effectiveness (RBE ≈ 2–3), and sharp Bragg peak dose distribution enables effective tumor eradication even in radioresistant histologies.

From a national perspective, the gradual implementation of C-ion RT in Indonesia is both strategically feasible and scientifically justified, provided that it is supported by structured capacity building, international collaboration, and strong regulatory governance. The development of a pilot C-ion RT facility could also catalyze growth in medical physics education, dosimetry research, and accelerator technology, thereby strengthening the country's healthcare resilience and scientific independence. Therefore, C-ion RT represents not only a clinical innovation but also a key opportunity to elevate Indonesia's position in the field of advanced radiotherapy and applied medical physics.

Recommendations

1. Future clinical research should incorporate larger multi -institutional patient cohort to strengthen statistical validity and better represent diverse clinical settings, particularly in developing countries such as Indonesia.
2. Further studies should explore the combination of C-ion RT with systemic therapy such as immunotherapy or molecular targeted agents to address distant metastasis and improve progression free survival outcomes.
3. Comprehensive feasibility and cost effectiveness assessments should be conducted to evaluate national readiness for adopting carbon-ion therapy, including infrastructure design, shielding requirements, accelerator technology, and maintenance sustainability.

Overall, the reviewed evidence demonstrates that carbon-ion radiotherapy offers a clinically effective and radiobiologically superior treatment option for radioresistant oral non-SCC. These recommendations are expected to guide future research, technology planning, and national policy development, supporting Indonesia's strategic pathway toward establishing particle-therapy-based cancer treatment and advancing the field of medical physics

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Author Contribution

Ringgit.P. performed literature analysis and drafted the initial manuscript. Raditya.F. conceptualized and supervised the study. Both authors revised and finalized the paper collaboratively

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