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ADVANCEMENT IN RADIOTHERAPY FOR HEAD AND NECK CANCER MANAGEMENT: A REVIEW

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ABSTRACT – *Objective:* This study aimed to evaluate the influence of side effects on the quality of life (QoL) and psychosocial functioning of patients with oropharyngeal cancer associated with Human Papillomavirus (HPV), and to explore de-escalation procedures in the treatment of head and neck cancer (HNC).

Materials and Methods: This study relied on systematic reviews and original research and focused on younger and older patients with HPV-induced oropharyngeal squamous cell carcinoma (OPSCC) undergoing modern radiotherapy (RT). This study aimed to analyze the impact of side effects on QoL and psychosocial functioning in these patients. De-escalation procedures and their effectiveness in the treatment of HPV-induced OPSCC were investigated. This study examined sophisticated image guidance, adaptive therapies, and precise delivery methods of modern RT.

Results: According to the findings, the side effects of modern RT in patients with HPV-induced OPSCC had a significant impact on their QoL and psychosocial functioning. Although the evidence regarding de-escalation procedures is still evolving, it suggests potential benefits in terms of reducing side effects and improving outcomes. The combination of modernization of RT, innovative systemic agents, and expanding therapeutic indications in the recurrent/metastatic context is also promising.

Conclusions: Patients with HPV-induced OPSCC undergoing modern RT face considerable challenges related to side effects that affect their QoL and psychosocial well-being. Therefore, exploring de-escalation procedures to mitigate these issues and to improve treatment outcomes is crucial. Further research is required to establish conclusive evidence regarding the effectiveness of de-escalation procedures and the optimal treatment approaches for HPV-induced OPSCC. Additionally, integrating RT modernization, innovative systemic agents, and expanding therapeutic indications holds great potential for advancing HNC treatment in recurrent/metastatic settings.

KEYWORDS: Radiotherapy, Head and Neck Cancer, De-escalation, Oropharynx, Nasopharynx.

INTRODUCTION

This article provides an overview of the present function of radiation in the care of head and neck cancer as well as recent advancements that have been made in the field. The promotion of cancer imaging technologies, software for treatment planning, and technology to administer radiation have had significant benefits for radiotherapy. Technologies and software serve as the principal therapeutic modalities for the management of head and neck cancer. The management of head and neck cancers often involves radiotherapy as the primary therapeutic technique. These advancements have improved both the local control of tumors and functional results. They have also made it possible to focus radiation more precisely on tumor-containing tissues, thereby reducing the amount of radiation absorbed by typical tissue structures. de-escalated radiotherapy, adaptive radiotherapy, sparing techniques, stereotactic ablative radiotherapy, radionics and radiobiology, re-irradiation, combined modality treatments, considerations for elderly patients, and how they have contributed to the care of head and neck cancer are elaborated in this review[1-3] (Figure 1).

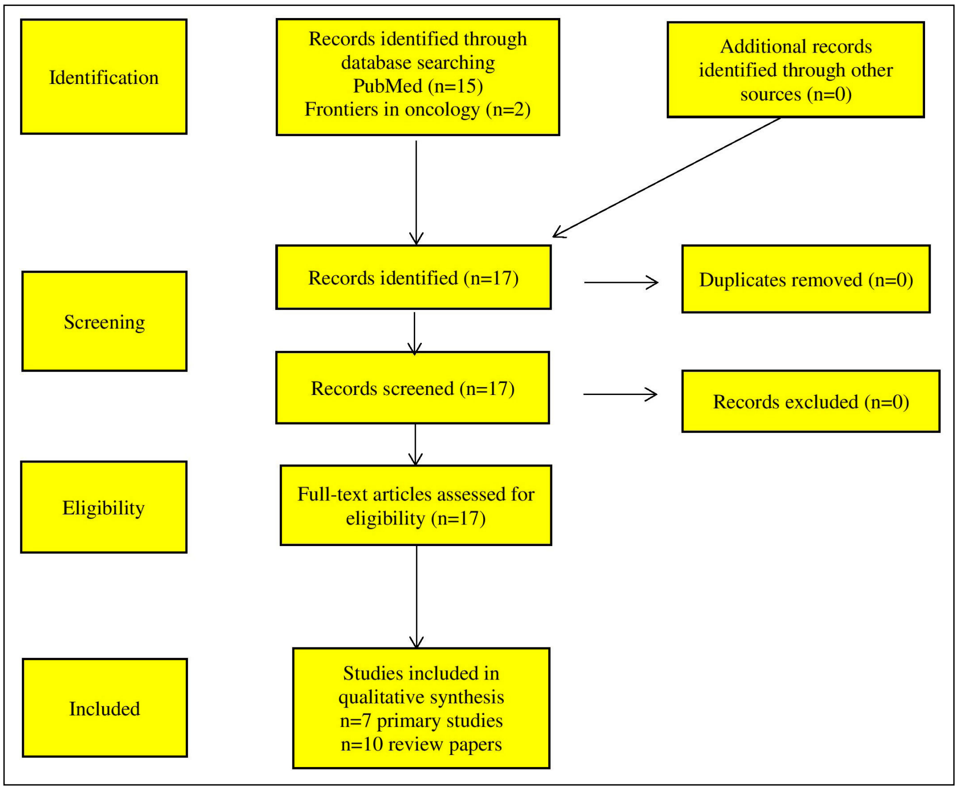

Figure 1. PRISMA Flow Diagram.

Modern radiotherapy (RT) is crucial for treating head and neck cancer (HNC). As the number of individuals undergoing treatment in these oncological settings increases, issues arising from therapy have become a known concern, despite patients' prioritization of being cured as their primary treatment objective. Being younger, healthier, and more responsive to treatment, patients with OPSCC or oropharyngeal cancer associated with Human Papillomavirus have particular relevance to this. Therefore, the influence of side effects on quality of life (QoL) and psychosocial functioning is a primary priority for HNC Researchers given their increased life expectancy. De-escalation procedures have only recently been developed, and although the evidence is inconclusive, they are growing. The de-escalation procedures apply, although not exclusively, to HPV-induced OPSCC caused by HPV. With the modernization of RT in terms of delivery and dosage, its combination with innovative systemic agents and expanding therapeutic indications in the recurrent/metastatic (R/M) context are undoubtedly at the forefront.

HPV related tumors and the role of radiotherapy

The incidence of head and neck tumors caused by human papillomavirus (HPV) has increased, particularly the expression of E6 and E7 oncoproteins, which have been on the rise due to high-risk HPV. Head and neck squamous cell carcinoma (HNSCC) is characterized by tumor hypoxia, which reduces the efficiency of radiotherapy[4]. HNSCC is aggressive and is more likely to occur. Tobacco and alcohol are the two risk factors for HNSCC are tobacco and alcohol [4]. Radiotherapy is negatively affected by hypoxia, which is characterized by low oxygen supply in the body. Hypoxia results from a lack of balance between the oxygen supply and demand. This may be a result of changes in tumor metabolism or poor perfusion of the vessels. Tumor hypoxia leads to radioresistance owing to reduced DNA damage in the tumor caused by a lack of oxygen[4]. Thus, the detection and quantification of severe hypoxia is crucial. Additionally, it is important to develop hypoxic-tumor targeted strategies[4]. Currently, the basic treatment for head and neck squamous cell carcinoma (HNSCC) comprises radiotherapy (RT) and chemotherapy. It is important to note that HPV-positive tumors are more radiosensitive than HPV-negative [4].

Reduced Doses of Radiation Therapy

Recent advancements in the technology used to administer radiation have made it possible to apply more accurate radiation targeting tissues containing tumors, thereby reducing the amount of radiation delivered to the typical tissue structures. The use of de-escalated radiation, which refers to treatment programs in which decreased doses are provided to target tissues while sparing nearby normal tissues, has been made possible by this development [5]. Computer-driven accelerators with high accuracy may be used to perform de-escalated radiotherapy, which limits radiation exposure to tumor-containing tissues. Furthermore, linear accelerators help to reduce radiation threads to healthy tissues. This is beneficial in lowering the risk of long-term adverse effects, while maintaining the same level of symptom management and increasing the probability of complete recovery (Figure 2).

Figure 2. Elekta Synergy (Digital Linear Accelerator). (Source: Nashik Cancer Centre, Maharashtra, India).

Adaptive radiotherapy

Adaptive radiotherapy is a type of radiotherapy in which the radiation dosage may be adapted in real time to the specific needs of the patient's anatomy or tumor response during treatment. This makes it possible to administer radiation with more precision, and it also makes it possible to consider any changes that may have occurred in the tumor. Adaptive radiotherapy aims to offer precision and accuracy in radiation performed on patients with cancer. This method has been shown to improve the local control rates and lower radiation toxicity[5-8] (Figure 3).

Figure 3. Elekta Synergy (Digital Linear Accelerator). (Source: Nashik Cancer Centre, Maharashtra, India).

Sparing Methods

Sparing methods use advanced imaging, patient management, and radiation delivery technologies to more accurately target tissues that contain tumors, while sparing nearby healthy tissues. One such approach, intensity-modulated radiotherapy (IMRT), minimizes radiation-induced long-term adverse effects of traditional radiotherapy. Intensity-modulated radiotherapy (IMRT) is an advanced radiation therapy that is used to treat cancer. Unlike traditional radiation therapy, IMRT uses computer-controlled linear accelerators to deliver precise doses of radiation to a tumor, while sparing the surrounding healthy tissues from radiation exposure. This is achieved by dividing the radiation beam into many small beams of different intensities, which can be adjusted to target the tumor from different angles. Intensity-modulated radiation therapy (IMRT) is the best radiation control for neck and head cancers, ranging from 75% to 39% ($p = 0.004$) 12 months after treatment[9]. Proton therapy can provide additional advantages to patients with tumors close to radiosensitive organs. Intensity-modulated radiation therapy (IMRT) reduces long-term adverse effects of conventional RT.

Stereotactic ablation and stereotactic body image-guided radiotherapy

Stereotactic ablative radiotherapy (SABR) and stereotactic body radiotherapy (SBRT) are used to treat tumors that cannot be resected surgically. However, SABR and SBRT have almost the same meaning, and are highly accurate radiation administration methods. This includes directing highly concentrated radiation beams to a specific tumor to expose healthy tissues in the surrounding area with as little radiation as possible. However, a subtle difference between SABR and SBRT is worth noting[9]. SABR is more commonly used to treat lung tumors, whereas SBRT is more commonly used to treat tumors in other body parts such as the liver, pancreas, prostate, and spine. SABR emphasizes the use of highly precise radiation delivery techniques to destroy tumor tissues, whereas SBRT emphasizes the use of high doses of radiation to achieve tumor control. The functionality of the method depends on the high-speed computerized software described in more detail in this study. Despite extensive discussion of pertinent advanced radiotherapies, it provides only a limited amount of information about SABR[8].

Antiblastic drugs and Head and Neck Cancer Chemosensitivity

Antiblastic drugs are commonly referred to as cancer drugs. These drugs are complicated and dangerous to handle, because they are highly toxic [10]. Furthermore, they are expensive and physicians should avoid wastage. It is estimated that a phial of antiblastic costs approximately 3000 euros [10]. Antiblastic drugs have negative side effects when used to treat neck and head cancer. Side effects include mucositis, dermatitis, and xerostomia (Table 1).

Table 1. Pharmacologic Therapies for Radiation.

Agent	Mechanism of Action	Dose/Frequency	Benefit
Palifermin	Recombinant human keratinocyte growth factor	120-180 μg/kg/wk, IV bolus	Reducing opioid use, average mouth and throat soreness scores; reduction in time to severe mucositis and medium duration of severe mucositis
Gabapentin	Reduction in neuropathic pain, exact mechanism unknown	300-900 mg T.D.S., PO	Reduction in opioid drug use
Pilocarpine	Cholinergic, parasympathomimetic agent with predominant muscarinic action	5 mg T.D.S., PO	Increase in unstimulated salivary flow rate; reduction in symptomatic xerostomia
Cevimeline	Cholinergic stimulant with selective action on the salivary gland M3-muscarinic receptors	30-45 mg T.D.S., PO	Increase in unstimulated salivary flow rate; improvement in xerostomia-related QoL
Amifostine	Thiol metabolite scavenges reactive oxygen species generated by ionizing radiation	200 mg/m^2 once daily as a 3-minute IV infusion, starting 15-30 min before standard fraction radiation therapy	Reduction in acute and late xerostomia in patients treated with RT alone. No significant benefit in patients receiving concurrent chemotherapy

The fields of Radiomics and Radiotherapy

Radiomics is a relatively recent branch of medical imaging that uses complex algorithms to analyze and derive quantitative characteristics from medical images. Radiomics is used to leverage imaging in the medical field and to provide more quantitative features that can offer an individual phenotype [11]. Figure 3 shows the different models associated with machine learning and physicians' understanding of radionics. These traits enhance patient stratification, predict therapeutic responses, and provide a more accurate immediate treatment. In combination with irradiation, radiation genomics has increased tumor control and reduced toxicity [11]. Because this technique is not detailed in sufficient depth in this article, it is not the primary focus of the discussion (Figure 4 and 5).

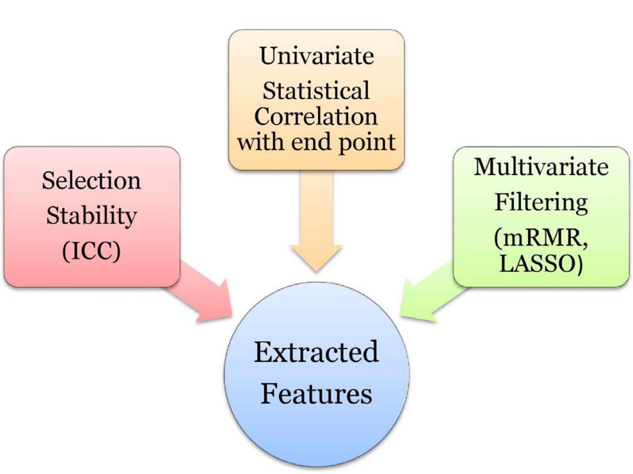

Figure 4. General feature selection process (Giraud et al 2019)[11].

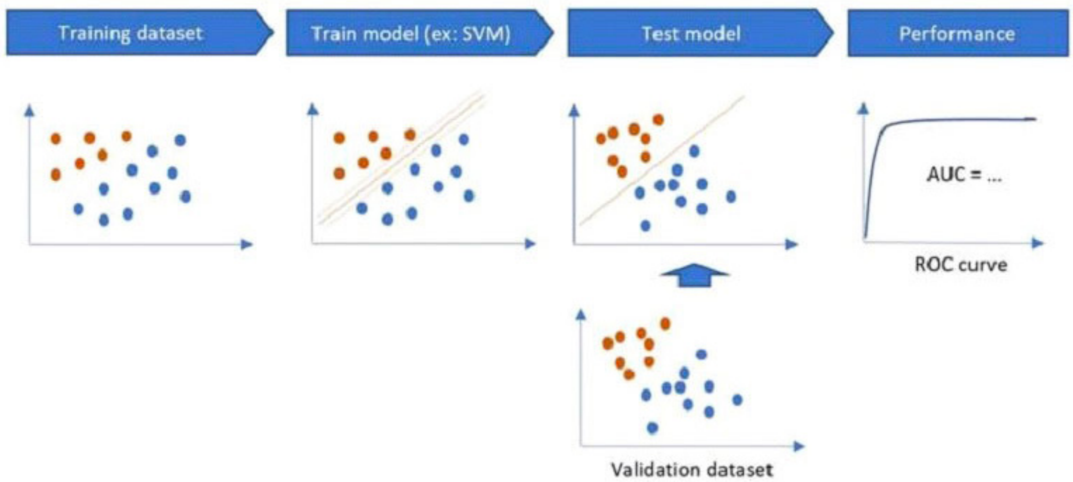

Figure 5. Graphical Representation (Giraud et al 2019)[11].

Re-irradiation

Re-irradiation involves administration of radiotherapy to a previously irradiated area of the body. This is a potential treatment option for patients who have experienced cancer recurrence in this area[12,13]. The success of re-irradiation depends on several factors, including the location and size of the tumor, the dose and volume of the initial radiation treatment, the interval between the initial radiation treatment and recurrence, and the patient's overall health. Re-irradiation can be local, regional, or metastatic during reoccurrence. Regional recurrence refers to the recurrence of cancer in the same area of the body where it was initially treated but not necessarily in the same location. For example, if a patient with breast cancer receives radiation therapy, regional recurrence can occur in the chest wall or lymph nodes[12,13]. On the other hand, local recurrence refers to the recurrence of cancer in the same location where it was initially treated. For example, if a patient received radiation therapy for a tumor in the lung, local recurrence would be a recurrence of cancer in the same area of the lung. Metastatic recurrence refers to the spread of cancer to other body parts of the body. For example, if a patient with prostate cancer received radiation therapy to the prostate, metastatic recurrence would occur in bones or other organs[12,13]. For instance, in one study, respondents were randomly selected based on age, sex, geographical residence, and originality.

Table 2. Random selection (Source: Study by Simone et al 2020)[12].

	Randomized patients		Non randomized patients	
	Organ preservation N=27	**Radical surgery N=28**	**Organ preservation N=61**	**Radical surgery N=7**
Age, years	65 (52–79)	65 (49–83)	74 (53–89)	69 (53–73)
Male	19 (70%)	17 (61%)	39 (64%)	4 (57%)
Female	8 (30%)	11 (39%)	22 (36%)	3 (43%)

Table 2 shows how the data spread after collection from individuals of diverse genders and ages. This shows that the non-randomized population had more elderly patients who required organ preservation than the randomized population did. Re-irradiation is a successful therapeutic option for certain patients and may enhance the percentage of patients whose cancer is under control [12]. Re-irradiation is a controversial therapeutic option because of concerns about high toxicity, variable dose administration, and lack of imaging modalities. Smaller tumor size, laryngeal and nasopharyngeal recurrence, and longer duration between repetitions are factors in choosing individuals. For affirmative margin resection and ECE, re-irradiation must be administered, and dose fractionation is essential for the radiotherapy of tumor cells [11]. Imaging modalities, such as PET and MRI should be used to detect carotid vascular ulceration, exterior sheathing, and fibrosis. Lengthy disease management may be achieved with proton treatment; however, dosage restrictions must be tailored based on past dose partitioning and duration since the last irradiation. Few investigations have employed brachytherapy re-irradiation because of fibrosis, osteoradionecrosis, and trismus. Systemic treatment, including re-irradiation, was combined with chemotherapy, but did not increased survival to eliminate microscopic illness and served as a radio photocatalyst.

De-escalated RT

Strategies including replacing, decreasing, or eliminating cytotoxic chemotherapy; lowering the dosage or volume of radiation; and incorporating less intrusive methods are now being researched and studied as potential treatments for cancer affecting sensitive body parts. Molecular markers, clinical risk assessments, adjuvant de-escalation predicated on pathological characteristics, and patient reactions to initial therapy are possible biomarkers that can be used to identify individuals for therapeutic de-escalation. With the ever-evolving therapies for locoregional head and neck cancers, the best patient evaluation and de-escalation approaches are paramount. Subsequently, two large phase III studies, De-ESCALaTE and RTOG 1016, failed to de-escalate therapy for HPV-associated head and neck cancer. Both trials showed that replacing cisplatin with cetuximab and radiation resulted in poor outcomes. This should alert those preparing for prospective evaluation studies in the clinical setting. Such trials must consider both toxicity and effectiveness outcomes.

According to histopathological studies, MRI and PER successfully differentiated between N0 and N+ patients. This is because PET/MRI has increased sensitivity and NPV compared with MRI alone. Furthermore, it is pathologically capable of detecting N0 patients and can be used to minimize the number of neck dissections, which may not be required[14].

Research in the Fields of Preclinical and Radiobiology

Research in preclinical settings and radiobiology is essential for radiotherapy research because it can provide insights into the biological processes by which radiation kills tumor cells, and may play a role in developing novel radiation therapies. Microbeam Radiotherapy (MRT) is an advancement in radiobiology and pre-clinical research. Despite exposure to high doses, such trends exhibit one-of-a-kind characteristics that affect the preservation of healthy tissues. It is also possible for these agents to boost the dosage administered to the intended tumors in the form of a succession of overlapping arrays. This can lead to vascular collapse and abnormal immunological reactions[7]. However, the practical use of these techniques is hindered by technological constraints. However, in conjunction with FLASH and GRID, they can potentially provide considerable increases in the curative ratio of spatially limited RT.

Combinations of Several Treatment Methods

Combined modality therapies, such as the simultaneous administration of chemotherapy and radiation, may enhance both locoregional control rates and overall survival in patients with head and neck cancer[15]. Cisplatin, paclitaxel, doxorubicin, fluorouracil, and cyclophosphamide are the commonly used chemotherapeutic drugs. Induction chemotherapy and cetuximab, an anti-epidermal growth factor receptor antibody, are two therapies that have been shown to enhance patient outcomes. Ferrari et al (2020)[16] explained that chemoradiotherapy could be effective if patients are affected by advanced neck and head cancers that are localized regionally, although its efficacy remains to be determined. Based on statistical data, for patients with TPF, it was better to adopt tolerance because 24.3% of the patients were unable to complete the treatment in the TPF arm compared to 35% who had to receive treatment in the PF arm [15]. However, toxicity was found to be a major issue in IC by recording a probability of up to 6% of toxic deaths[16]. Although this new method is among the most sophisticated procedures available for radiation treatment, more evidence is needed to support this.

Patients Who Are Elderly

As elderly people are often omitted from trials and clinical research, there is a lack of evidence regarding the effectiveness and safety of radiation therapies in patients aged ≥ 60 years. However, current research suggests that older adults may benefit from radiation treatments that are correctly targeted to their needs and that these patients may achieve great results. Elderly individuals should not be exposed to rational treatments such as radiotherapy, as this could affect their physiological reservation capacity[17]. In this qualitative study, radiation therapy was administered to 68 participants. The response rates to other treatment therapies including adaptive therapy, sparing methods, stereotactic ablation, and stereotactic body radiotherapy were 47%, 28%, 36%, and 30%, respectively[17] (Figure 6).

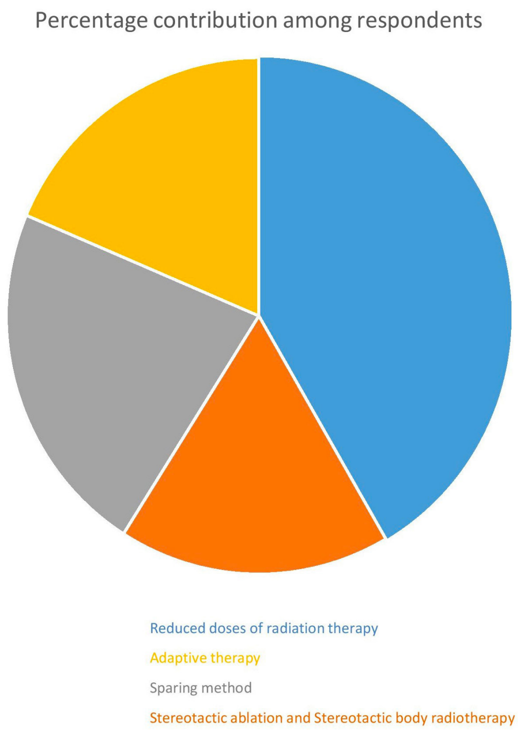

Figure 6. Percentage of contribution among respondents.

CONCLUSIONS

Modern improvements in the technology used to administer radiation have made it feasible to target tissues carrying tumors more precisely, thereby reducing the amount of radiation supplied to unusual tissue structures. During treatment, adaptive radiotherapy adjusts the radiation dose according to the unique requirements of the patient's tumor. Sparing approaches combine sophisticated imaging, patient management, and radiation delivery technology to more precisely target radiotherapy to tissues that contain malignancies, while sparing neighboring healthy tissues. The radiation-induced long-term severe adverse effects of conventional radiotherapy have been significantly reduced by intensity-modulated radiotherapy (IMRT).

Stereotactic ablation and body radiation (SABR) may be used to treat malignancies that cannot be surgically removed. Reirradiation is an effective treatment option for certain patients and preclinical and radiobiological research is a crucial part of radiotherapy research. Technological advancements have resulted in rapid changes in the treatment and assessment of head and neck cancer. For instance, reduced doses of radiotherapy have shown significant effects on treatment compared with other therapeutic techniques.

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The authors declare no conflicts of interest.

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MK, RJ, RS, and LS contributed to the planning of the design implementation and data collection of the article.

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