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CLINICAL REVIEW

Influence of time between surgery and adjuvant radiotherapy on prognosis for patients with head and neck squamous cell carcinoma: A systematic review

Kaiyuan Sun MSc[1] | **Jia Yan Tan BBiomedSc**[1] | **Peter James Thomson MD, PhD, DDSc**[2] | **Siu-Wai Choi PhD**[3]

[1]Division of Oral and Maxillofacial Surgery, Faculty of Dentistry, The University of Hong Kong, Hong Kong, China

[2]College of Medicine and Dentistry, James Cook University, Queensland, Australia

[3]Department of Orthopaedics and Traumatology, Queen Mary Hospital, Pokfulam, Hong Kong, China

Correspondence
Siu-Wai Choi, Department of Orthopaedics and Traumatology, 5/F Professorial Block, Queen Mary Hospital, Pokfulam, Hong Kong, China.
Email: htswchoi@hku.hk

Abstract

The timing of postoperative radiotherapy following surgical intervention in patients with head and neck cancer remains a controversial issue. This review aims to summarize findings from available studies to investigate the influence of time delays between surgery and postoperative radiotherapy on clinical outcomes. Articles between 1 January 1995 and 1 February 2022 were sourced from PubMed, Web of Science, and ScienceDirect. Twenty-three articles met the study criteria and were included; ten studies showed that delaying postoperative radiotherapy might negatively impact patients and lead to a poorer prognosis. Delaying the start time of radiotherapy, 4 weeks after surgery did not result in poorer prognoses for patients with head and neck cancer, although delays beyond 6 weeks might worsen patients' overall survival, recurrence-free survival, and locoregional control. Prioritization of treatment plans to optimize the timing of postoperative radiotherapy regimes is recommended.

KEYWORDS

head and neck squamous cell carcinoma, patient prognosis, postoperative radiotherapy, radiotherapy, time interval

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy worldwide. Global data from 2020 showed that there were approximately 931 931 new cases and 467 125 mortalities from malignancies arising from the lip, oral cavity, larynx, oropharynx, salivary glands, hypopharynx, and nasopharynx sites; a 5% increase compared to data collected in 2018.[1,2] HNSCC is often linked to habitual and lifestyle factors, such as tobacco smoking, alcohol drinking, betel nut chewing, and poor dietary habits.[3] High-risk human papillomaviruses (HPV) infection has also been implicated in malignancies arising in the oropharynx subsite.[4–7]

Curative surgery remains the principal treatment modality for patients presented with resectable tumors. The delivery of adjuvant postoperative radiotherapy, or combination chemoradiotherapy, is determined by the initial disease staging and/or the aggressiveness of the tumor as confirmed by histopathological examination of

the resected specimen and involvement of draining cervical lymph nodes. While advances in patient management and therapeutic regimens have greatly improved patient's quality of life, the overall prognosis for patients with HNSCC remains poor with approximately 50% survival rate within 5 years of diagnosis, surgery, and postoperative radiotherapy.[2,8]

Delays in postoperative radiotherapy are often a result of patient management issues in many health care systems. The American National Comprehensive Cancer Network (NCCN) recommends that planned postoperative radiotherapy (PORT) should commence within 42 days of surgery,[9] while the Dutch Head and Neck Society advise commencement by 30 postoperative days.[10]

The optimal time interval between surgery and PORT remains controversial, however. While some studies have reported that delayed commencement, greater than 30 days postsurgery, showed little adverse effects on patient prognoses for breast, lung, colorectal and pancreatic cancer,[11–15] others have observed that treatment delays were associated with poor survival outcomes, especially for bladder, breast, colorectal, lung, cervix, and head and neck cancers.[16] Thus, it remains unclear whether delaying the commencement of PORT harms patients with HNSCC, especially those with advanced disease.[17]

In recent years, there has been a paradigm shift towards personalizing treatment plans using newly available algorithms based upon patient-specific variables. Determining optimum treatment intervals between surgery and adjuvant postoperative cancer therapies may contribute significantly to patient-centered algorithms in treatment planning.

This systematic review thus aims to summarize existing research findings in order to clarify the relevance of time intervals between surgical treatment and PORT on patient prognosis for HNSCC.

2 | METHODS AND MATERIALS

The protocol of this study has been registered in PROSPERO.

2.1 | Search strategy

PubMed, Web of Science database, and ScienceDirect were searched to retrieve original articles from January 1995 to February 2022. Keywords such as "adjuvant therapy" OR "adjuvant treatment" OR "adjuvant care" OR "radiotherapy" OR "radiation therapy" OR "radiotherapy treatment" OR "systemic therapy" OR "immunotherapy" OR "hormone therapy" OR "chemotherapy" AND "head and neck cancer" OR "head and neck carcinoma squamous cell" OR "head and neck squamous cell carcinoma" OR "head and neck squamous cellular carcinoma" OR "HNSCC" OR "oral squamous carcinoma cell" OR "OSCC" OR "Oral cavity cancer" OR "Epidermoid carcinoma" AND "prognosis" OR "after surgery" OR "postoperative" AND "time factor" OR "effect of time" OR "impact of time" OR "interval" OR "treatment delay" OR "time to initiation" OR "package time" were included in the search.

All retrieved and relevant studies were searched by two investigators independently, then merged into Endnote 20. Study selection was conducted in a two-stage process; titles and abstracts were initially screened for studies relevant to this review, then full texts were further evaluated to ensure fulfillment of the set criteria. Hand-searching of articles was conducted to ensure inclusion of studies that may have been missed during the primary database search.

2.2 | Eligibility criteria

Eligibility for inclusion was set according to the following criteria: (1) patients diagnosed with head and neck cancer, (2) patients receiving radiotherapy postsurgery and (3) studies have reported the influence between different postoperative time intervals or package times (package time being the collective term referring to postoperative interval time and radiotherapy time) and adjuvant treatment outcomes in patients with head and neck cancer. Conference proceedings, narrative reviews, letters, and studies based on animal experiments and neoadjuvant chemoradiation (radiation before surgery) were excluded from this review.

2.3 | Quality criteria

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies (which were not randomized) and case–control studies. Quality assessment of all included studies was undertaken independently by two investigators. Any inter-reviewer disagreements that arisen after the scale was applied were resolved following a discussion with a third reviewer until consensus was obtained.

2.4 | Information extraction

Information regarding study population and number of patients, year of publication and data collection period, study design, and disease sites were collected from all

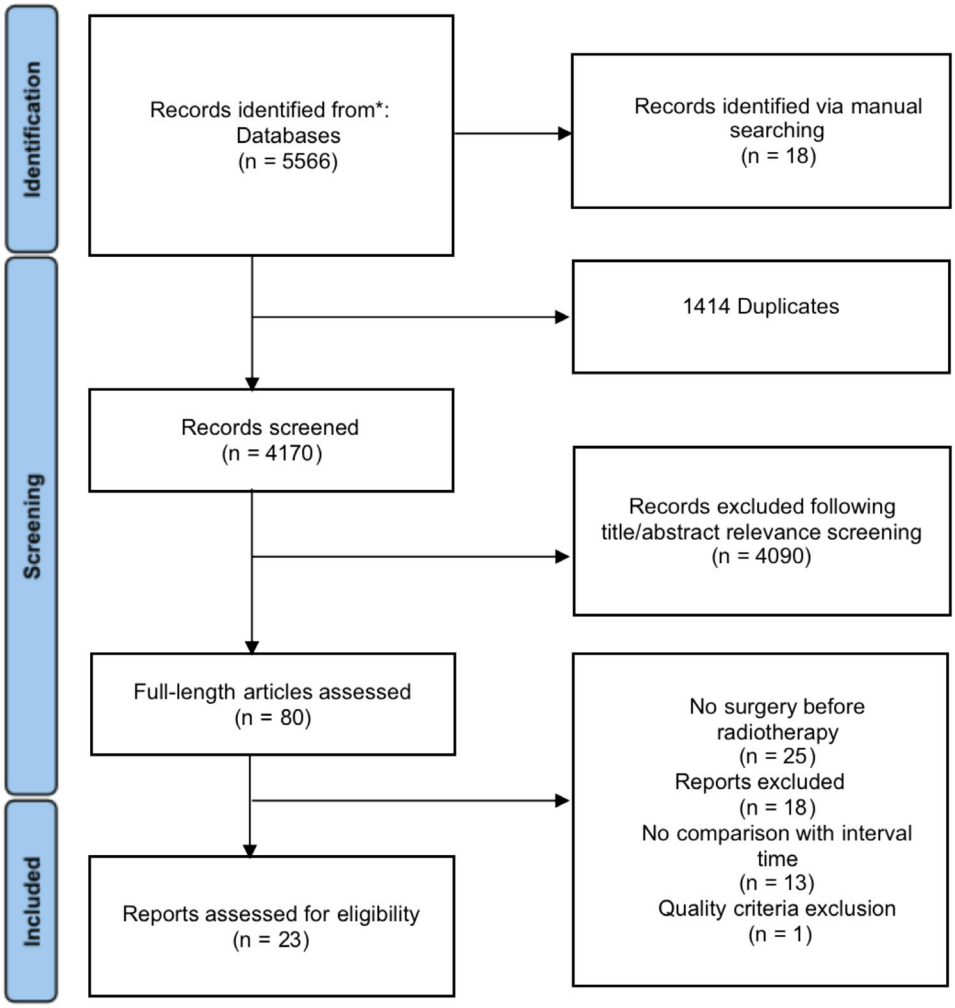

FIGURE 1 Preferred reporting items for systematic reviews: PRISMA flowchart[18] [Color figure can be viewed at wileyonlinelibrary.com]

available studies. Information on the influence of time interval between surgical treatment and adjuvant radiotherapy on patient prognosis was collated and summarized.

3 | RESULTS

3.1 | Study selection

An initial search returned a total of 5566 articles. After deduplication, initial screenings of titles and abstracts were performed on 4170 articles. Eighty full texts were assessed based on the set criteria. A total of 23 papers were identified and included in this review (Figure 1).

The Newcastle-Ottawa Scale (NOS) was utilized to evaluate the 24 articles and the results are shown in Table 1.[19–42] Articles with a score of six and above out of nine were included in this review. After evaluation, the highest score was 9, and the lowest was 6. Twenty-three articles fulfilled the set criteria; one article with a score below 6 was excluded.[19] A total of 19 studies within the selected 23 publications had or contained the most common subsite recorded in oral squamous cell carcinoma (OSCC) in HNSCC.

Studies selected for this study were mainly conducted in the United States, Germany, and the Netherlands. Data for these studies were collected either from population databases or single health care institutions. Seven out of the twenty-three included studies used the same database, the National Cancer Data Base (NCDB). These studies accounted for 313 547 patients among a total of 328 133 patients. Therefore, it is possible that some patients' data may be duplicated and reported in more than one study.

3.2 | Study description

All twenty-three included articles were retrospective studies (Table 2).[20–42] Main lesion sites were observed in the oral cavity, oropharynx, hypopharynx, and larynx. Reported HNSCC and OSCC cases in these studies were diagnosed between 1964 and 2020.

TABLE 1 Risk of bias

Study	Item and score								
	Representees of the exposed (1)	Selection of the nonexposed (1)	Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Compare the ability of the basis of the design or analysis (2)	Assessment of outcome (1)	Was follow-up long enough for outcomes to occur (1)	Adequacy of follow up (1)	Score (9)
Brockmeyer et al.[19]	1	0	1	1	0	1	1	0	5
Fujiwara et al.[20]	1	1	1	1	2	1	0	0	8
Chen et al.[21]	1	1	1	1	2	1	0	0	7
Harris et al.[22]	1	0	1	1	2	1	1	1	8
Graboyes et al.[23]	1	0	1	1	2	1	0	0	6
Sievert et al.[24]	1	1	1	1	2	1	1	0	8
Shaikh et al.[25]	1	0	1	1	2	1	0	0	6
Balk et al.[26]	1	1	1	1	2	1	0	0	7
Le Tourneau et al.[27]	1	1	1	1	2	1	1	1	9
Cheng et al.[28]	1	1	1	1	2	1	0	0	7
Cramer et al.[29]	1	0	1	1	2	1	0	1	7
Langendijk et al.[30]	1	1	1	1	2	1	0	0	7
Franco et al.[31]	1	1	1	1	2	1	0	0	7
Parsons et al.[32]	1	0	0	1	2	1	0	1	6
Marshak et al.[33]	1	1		1	2	1	1	1	8
Muriel et al.[34]	1	1	1	1	2	1	1	0	8
Suwinski et al.[35]	1	1	1	1	2	1	0	1	8
Mazul et al.[36]	1	0	1	1	2	1	0	0	6
van Harten et al.[37]	1	0	1	1	2	1	0	0	6
Tam et al.[38]	1	0	1	1	2	1	1	1	8
Dixit et al.[39]	1	1	1	1	2	1	1	1	9
Trotti et al.[40]	0	0	1	1	2	1	1	1	7
Rosenthal et al.[41]	1	1	1	1	2	1	1	0	8
Santos and Monteiro[42]	1	1	1	1	2	1	0	1	8

TABLE 2 Summary of study quality

Author	Region	Period	Sites	Type of cancer	Study design	Data sources	Sample size	Quality of study
Brockmeyer et al.[19]	Germany	1995–2005	Cheek/lip, tongue, alveolar process/jaw, mouth floor, palate/oropharynx	OSCC, HNSCC	Case control study	Not specified	106	5 (excluded)
Fujiwara et al.[20]	USA	1998–2011	Oral cavity	OSCC	Cohort study	NCDB	4868	8
Chen et al.[21]	USA	2008–2016	Oral cavity	OSCC	Cohort study	Department of Otolaryngology – Head and Neck Surgery	132	7
Harris et al.[22]	USA	2004–2013	Tonsil, nontonsil oropharynx, oral cavity, larynx, hypopharynx	OSCC, HNSCC	Cohort study	NCDB	25 216	8
Graboyes et al.[23]	USA	2006–2014	Oral cavity, oropharynx, hypopharynx, larynx	OSCC, HNSCC	Cohort study	NCDB	41 291	6
Sievert et al.[24]	Germany	2000–2016	Oropharynx	HNSCC	Cohort study	Department of Otorhinolaryngology	157	8
Shaikh et al.[25]	USA	1998–2011	Tonsil, hypopharynx, larynx, oropharynx, tongue	OSCC, HNSCC	Cohort study	NCDB	19 531	6
Balk et al.[26]	Germany	2007–2020	Tonsils, bilaterally, tongue base, hypopharynx	OSCC, HNSCC	Cohort study	A Single Tertiary Referral and Academic Cancer Center	131	7
Le Tourneau et al.[27]	France	1990–1998	Oral cavity, oropharynx, larynx, hypopharynx	OSCC, HNSCC	Cohort study	Sainte-Barbe clinic and Paul Strauss Comprehensive Cancer Center	308	9
Cheng et al.[28]	Taiwan	2007–2015	Oral cavity, lip, tongue, gingiva, floor of mouth, hard palate, buccal, other forms of oral cancer	OSCC, HNSCC	Cohort study	TCR Database	8986	7
Cramer et al.[29]	USA	2004–2014	Oral cavity, oropharynx, larynx, hypopharynx	OSCC, HNSCC	Cohort study	NCDB	76 853	7

(Continues)

TABLE 2 (Continued)

Author	Region	Period	Sites	Type of cancer	Study design	Data sources	Sample size	Quality of study
Langendijk et al.[30]	Netherlands	1985–2000	Mucosal surfaces of the oral cavity (excluding the lip)	OSCC	Cohort study	VU University Medical Center	217	7
Franco et al.[31]	Brazil	2009–2015	Oral cavity, oropharynx, larynx	OSCC, HNSCC	Cohort study	Single center	168	7
Parsons et al.[32]	USA	1964–1993	Oral cavity	OSCC	Cohort study	University of Florida's Department of Radiation Oncology	135	6
Marshak et al.[33]	Israel	1979–1994	Larynx	HNSCC	Cohort study	Rabin Medical Center	44	8
Muriel et al.[34]	Spain	1985–1995	Oral cavity, oropharynx, hypopharynx, larynx, supraglottic larynx	OSCC, HNSCC	Case control study	Department of Radiation Therapy at Granada University Hospital	214	8
Suwinski et al.[35]	USA	1980–1997	Larynx, other	HNSCC	Cohort study	Center of Oncology in Gliwice	868	7
Mazul et al.[36]	USA	2007–2015	Oral cavity, hypopharynx, Larynx, oropharynx	OSCC, HNSCC	Cohort study	NCDB	129 055	6
van Harten et al.[37]	Netherlands	1990–2011	Oral cavity, hypopharynx, larynx, oropharynx	OSCC, HNSCC	Cohort study	The Netherlands Cancer Institute (NCI)	2493	6
Tam et al.[38]	USA	2004–2012	Oral cavity, hypopharynx, larynx, oropharyngeal	OSCC, HNSCC	Cohort study	NCDB	16 733	8
Dixit et al.[39]	Bahrain	1989–1993	Buccal mucosa	OSCC	Cohort study	The Gujara Cancer and Research Institute	176	9
Trotti et al.[40]	USA	1988–1990	Laryngopharynx, oral cavity, oropharynx	OSCC, HNSCC	Cohort study	Multicenter	32	7
Rosenthal et al.[41]	USA	1992–1997	Oral cavity, oropharynx, hypopharynx, larynx, parotid, occult primary, sinus	OSCC, HNSCC	Cohort study	University of Pennsylvania Medical Center	208	8
Santos and Monteiro[42]	Portugal	2012–2016	Pyriform sinus, posterior, pharyngeal wall, post cricoid region	HNSCC	Cohort study	Oncological Tertiary Center	211	8

TABLE 3 Comparison of overall survival

	Overall survival (OS)		
Studies	**Follow-up time**	**Hazard ratio (95% CI) or overall survival rate (%)**	***p*-value**
Fujiwara et al.[20]	5 years	≤50 days: 1.00 ≥64 days: 0.96 (0.81–1.15)	$p = 0.69$
Chen et al.[21]	Not specified	≤6 weeks: 1.00 >6 weeks: 1.34 (0.53–3.36)	$p = 0.54$
Harris et al.[22]	Not specified	≤42 days: 1.00 43–49 days: 0.98 (0.93–1.04) ≥50 days: 1.07 (1.02–1.12)	43–49 days: $p > 0.05$ ≥50 days: $p < 0.05$
Graboyes et al.[23]	Not specified	≤4 weeks: 0.84 (0.77–0.92) 4–5 weeks: 0.84 (0.76–0.92) 5–6 weeks: 1.00 6–7 weeks: 1.15 (1.06–1.25) 7–8 weeks: 1.26 (1.16–1.38) 8–10 weeks: 1.39 (1.28–1.51) ≥10 weeks: 1.46 (1.35–1.58)	$p < 0.01$
Sievert et al.[24]	5 years	≤50 days: 85.7% >50 days: 87.4%	$p = 0.588$
Shaikh et al.[25]	Not specified	Hazard ratio: <8 weeks: 1.00 ≥8 weeks: 1.21 (1.01, 1.44)	$p = 0.0347$
Balk et al.[26]	5 years	≤55 days: 77% (7/11) >55 days: 64% (4/11)	$p = 0.281$
Le Tourneau et al.[27]	5 years	≤44 days: 36% >44 days: 35%	$p = 0.84$
Cheng et al.[28]	5 years	0–4 weeks: 1.00 4–5 weeks: 0.92 (0.83–1.01) 5–6 weeks: 0.92 (0.83–1.01) 6–7 weeks: 0.98 (0.86–1.11) >7 weeks: 1.07 (0.96–1.20)	4–5 weeks: 0.244 5–6 weeks: 0.429 6–7 weeks: 0.823 >7 weeks: 0.853
Cramer et al.[29]	Not specified	≤6 weeks: HR, 0.92 (0.89–0.96) >6 weeks: 1.00	$p < 0.05$
Mazul et al.[36]	5 years	<28 days: 1.00 28–56 days: 1.04 (0.98–1.1) >56 days: 1.01 (0.93–1.1)	28–56 days: $p = 0.199$ >56 days: $p = 0.78$
van Harten et al.[37]	5 years	Univariate 0–30 days: 1.00 >30 days: 0.870 (0.749–1.009) Multivariate 0–30 days: 1.00 >30 days: 0.838 (0.708–0.992)	Univariate: $p > 0.05$ Multivariate: $p < 0.05$
Tam et al.[38]	Not specified	≤6 weeks: 1.00 >6 weeks: 1.10 (1.04–1.16)	$p < 0.001$

Thirteen articles investigated overall survival after comparing the effect of time between surgery and the initiation of after-surgery radiotherapy (TTI). Eight studies compared time and locoregional control. Four studies mapped the relapse-free survival rates.

3.3 | Overall survival

A total of 13 studies compared the overall survival of patients with HNSCC and the time interval between surgery and TTI (Table 3).[20–29,36–38]

TABLE 4 Comparison of locoregional control

Studies	Locoregional control		
	Follow-up time	Locoregional control rate (%)	*p*-value
Le Tourneau et al.[27]	2 years	≤44 days: 81% >44 days: 73%	$p = 0.2$
Langendijk et al.[30]	3 years	<6 weeks: 79% 6–8 weeks: 73% >8 weeks: 73%	$p = 0.0004$
Franco et al.[31]	Not specified	<92 days: 62.5% >92 days: 64.3%	$p = 0.95$
Parsons et al.[32]	5 years	20–50 days: 84% (48/57) ≥50 days: 76% (16/21)	$p = 0.3$
Marshak et al.[33]	Not specified	≤45 days: 89% >45 days: 76%	$p = 0.2539$
Muriel et al.[34]	5 years	≤50 days: 83 ± 6.6% >50 days: 68 ± 6.5%	$p = 0.02$
Dixit et al.[39]	3 years	<30 days: 26% (9/35) >30 days: 65% (17/26)	$p = 0.0019$
Trotti et al.[40]	6 years	≤4 weeks: 0/10 (0%) >4 weeks 10/22 (45%)	$p = 0.013$

Eight of the thirteen articles showed that overall survival was not affected by TTI.

Three articles found no significant differences in overall survival between interval length at 42–44 days and less than 42–44 days.[21,22,27] While three studies[20,24,26] reported that time intervals of 50–55 days and above also had no effect on survival compared to patients treated before 50–55 days postsurgery.

Two studies also demonstrated no statistical differences in outcomes regardless of whether patients were treated within 4 weeks, 4–5 weeks, 5–6 weeks, greater than 7 weeks, or greater than 8 weeks postsurgery.[28,36]

In contrast, three studies showed that when comparing patients who received adjuvant therapy at earlier than 6 weeks or at the recommended 6 weeks, worse overall survival was associated with a gradual increase in times greater than 6 weeks.[23,29,38]

Another two studies showed that a delay in the commencement of adjuvant radiotherapy for more than 7 weeks and 8 weeks were significantly associated with poorer overall survival.[22,25]

It is worth noting that it has been shown in one study[37] that short intervals of less than 30 days were associated with worse survival and that intervals greater than 90 days were not associated with survival impairment.

Overall, whether patients who received radiotherapy earlier than 6 weeks after surgery exhibited significantly different outcomes than those treated at 6 weeks is highly controversial, but the majority opinion is that there is a significant association between interval length and survival.

3.4 | Locoregional control

Eight studies[27,30–34,39,40] reported associations between locoregional control and TTI (Table 4).

Three studies demonstrated that patients' delay in commencing postoperative radiotherapy was significantly associated with worse locoregional control.

In Muriel's study,[34] patients who had radiotherapy within 50 days had a 15% increased chance of better locoregional control, when compared to patients who were given radiotherapy after more than 50 days upon surgery. Another two studies showed that TTI greater than 4 weeks or 30 days could lead to a significantly higher locoregional failure rate (i.e., within the field borders) than TTI of 4 weeks and less.[39,40]

The remaining five studies[27,30–33] reported no statistically significant associations between starting postsurgical radiotherapy and locoregional control of more than 8 weeks (vs. less than 6 weeks or 6–8 weeks), greater than 92 days (vs. 92 days or less), 50 days or more (vs. 20–50 days), more than 44 days (vs. 44 days or less), and greater than 45 days (vs. 45 days or less).

3.5 | Relapse-free survival rate

Four studies[22,28,31,35] compared relapse-free survival between patients who started postoperative radiotherapy at different time intervals (Table 5).

A detailed breakdown of the time intervals was presented by Cheng et al.[28] No significant correlation between

TABLE 5 Comparison of relapse-free survival rate

	Relapse-free survival		
Studies	**Follow-up time**	**Hazard ratio (95% CI) or relapse-free survival rate (%)**	***p*-value**
Chen et al.[21]	Not specified	Hazard ratio or odd ratio ≤6 weeks: 1.00 >6 weeks: 2.42 (1.13–5.21)	$p = 0.02$
Cheng et al.[28]	5 years	Hazard ratio (95% CI) 0–4 weeks: 1.00 4–5 weeks: 0.97 (0.84–1.12) 5–6 weeks: 0.92 (0.81–1.06) 6–7 weeks: 1.05 (0.88–1.25) >7 weeks: 1.16 (0.99–1.35)	4–5 weeks: $p = 0.672$ 5–6 weeks: $p = 0.256$ 6–7 weeks: $p = 0.552$ >7 weeks: $p = 0.061$
Franco et al.[31]	Not specified	≤92 days: 75.4% >92 days: 66.4%	$p = 0.377$
Suwinski et al.[35]	5 years	<30 days: 76% 30–60 days: 72% 61–90 days: 67% >90 days: 61% Relative risk: 1.22	$p = 0.041$

the length of TTI and 5-year relapse free survival (HR = 1.00 for TTI of 0–4 weeks; HR = 0.97 for TTI of 4-5 weeks [0.84–1.12]; HR = 0.92 for TTI of 5–6 weeks [0.81–1.06]; HR = 1.05 for TTI of 6–7 weeks [0.88–1.25]; HR = 1.16 for TTI of >7 weeks [0.99–1.35]) was observed. A study by Franco et al.[31] also demonstrated no significant relationship between relapse-free survival and TTI of more than 92 days versus 92 days and less.

Two studies[21,35] did show a statistically significant difference between TTI and relapse-free survival. Compared to those who received postsurgical treatment earlier than 90 days, patients who received radiotherapy after more than 90 days presented with poorer relapse-free survival.[35] In a more recent analysis, patients receiving radiation therapy more than 6 weeks postsurgery also had a significantly worse relapse-free survival.[21]

4 | DISCUSSION

The results of this systematic review are limited to some extent by the small number of available studies, variable study sample sizes, retrospective study design, and single treatment site locations. Nonetheless, it appears that commencing PORT as early as 4 weeks postsurgery as recommended did not deliver more favorable patient prognoses than treatment at 6 weeks, although delays beyond 6 weeks or greater than 8 weeks may be associated with poorer overall survival, recurrence-free survival, and locoregional control.[21–23,25,29,34,35,38–40] Furthermore, in addition, we found a total of three studies with multiple periods. Two studies showed that OS and RFS showed a significant and sustained decline along with the constant delay in radiotherapy.[23,28,35]

In a randomized controlled trial, it was observed that prolonged TTI showed significant effects on both locoregional control and overall survival for patients receiving conventional fractionated RT. This study also showed that the use of accelerated fractionated RT resulted in better overall survival and locoregional recurrence compared with conventional delayed RT.[43] Similar findings have now been reported in other studies, and accelerated RT techniques may to, some extent, mitigate the harm of delayed treatment.[31,39,40]

The causes of PORT delay are, of course, diverse. For example, different institutions or health care systems have their own practices, such differences might be apparent in the scheduling of patients for radiation therapy. Moreover, patient's access to radiotherapy maybe disrupted by issues such as travel distance and insurance referral.[44,45] A time delay in one or more steps on the pathway to therapy may result in an eventual delay in patient receiving ultimate care.[46] At the patient level, those with advanced disease or underlying medical complications may require more postoperative recovery time for wounds to heal. The time required for wound healing is patient-specific and involves many factors, including presence of chronic comorbidities such as diabetes. Patients can only undergo postoperative radiotherapy when they are deemed medically fit, and the time taken for patients to reach this stage may not fall within the recommended timeframe of 6 weeks. Patient hesitancy

and wish to seek second opinions may also affect the radiotherapy treatment schedule.[22,34,39] In addition to the reasons mentioned above, fragmentation is also of concern, where patients undergo different surgical and radiation treatments at different institutions, which is typical and associated with delayed PORT initiation.[17,45,47]

Notably, the American College of Surgeons Commission on Cancer recently announced the first-quality metric regarding the timing of adjuvant radiation therapy: for patients with surgically managed head and neck squamous cell carcinoma (HNSCC) disease, postoperative radiotherapy (PORT) is to be initiated <6 weeks after surgical treatment. However, the conclusions of the our review in this area are consistent with this quality metric.[48]

Malignancies arising from the head and neck and oral are highly aggressive and multifactorial. Hence, the tumor's distinct entities should be considered, especially in this era of precision medicine.[49] Therefore, future studies seeking to provide an evidence base for clinicians to use as a guideline when deciding when to commence with postoperative radiotherapy should also consider these factors.

Based on patient-specific factors, future research can explore models for prioritizing and modeling postoperative radiotherapy. For example, SWALIS model[50] and a model of patient prioritization proposed in 2012[51] may help clinicians differentiate and prioritize the needs of patients. These models can be stratified based on main prognostic factors such as the primary tumor site, treatment setting, surgical situation, and tumor curability. The application of prioritization models to postoperative radiotherapy systems stratifies patients according to clinical criteria and diagnosis time, which enables clinicians to make informed choices about the urgency of starting radiotherapy and to minimize delays caused by patient referrals or other factors.

Among them, the SWALIS model[50] is more mature and clinically applicable. To simulate the impact of the prioritization scoring algorithm, the SWALIS Steering Committee selected 10 representative surgical units within the hospital and formed a scientific committee. The committee followed the principle of simplification in setting up the system and adopted the modified Italian Government urgency related groups (URG) as the criteria for clinical assessment. Additionally, the committee also redefined relevant definitions. The final priority URG was associated with the urgency factor according to basic information registered by the patient (definite/suspected diagnosis, expected surgical procedure, URG, date/time). Different priority scores were obtained based on the degree of urgency of the patient and the increases in clinical need in increasing time. The corresponding waiting time will then be provided to patients. The SWALIS pre-admission model underwent a 3-year model experimental phase, using a standardized prioritization method that can be applied to all patients suitable for elective surgery. This allows effective monitoring of waiting lists.[50]

5 | CONCLUSION

Despite controversies mentioned in the literature, it is recommended that PORT for patients with OSCC and HNSCC should commence no later than 6 weeks after surgery as better clinical outcomes in terms of overall survival, recurrence-free survival, and locoregional control were observed. Postsurgery intervals longer than 6 weeks should be avoided. For patients who are unable to commence PORT within the 6-week timeframe, there is evidence that accelerated RT regimes can compensate for any harm caused by long postoperative intervals.[39,40]

AUTHOR CONTRIBUTIONS

Siu-Wai Choi conceived the study. Kaiyuan Sun conducted articles screening work. Siu-Wai Choi and Jia Yan Tan provided supervision and validation. Kaiyuan Sun completed data extraction and processing and wrote the original draft of the manuscript. Jia Yan Tan, Siu-Wai Choi, and Peter James Thomson critically revised the manuscript. All authors approved the final manuscript version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

No new data was generated or analyzed in this study. Thus, data sharing is not applicable.

ORCID

Kaiyuan Sun https://orcid.org/0000-0002-5177-3471
Siu-Wai Choi https://orcid.org/0000-0002-8189-790X

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