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內文：

I. Introduction:

1. Acute toxicity of RT: moist desquamation, skin erythema, loss of taste, and mucositis (resolve with time);Late toxicity: radiation caries, trismus, xerostomia, myelitis, skin fibrosis, and osteoradionecrosis (ORN);recurrent & ORN are the most dreaded thing,
2. New advances in RT;CCRT ;new delivery of RT;
3. Historic ORN incidence:

□

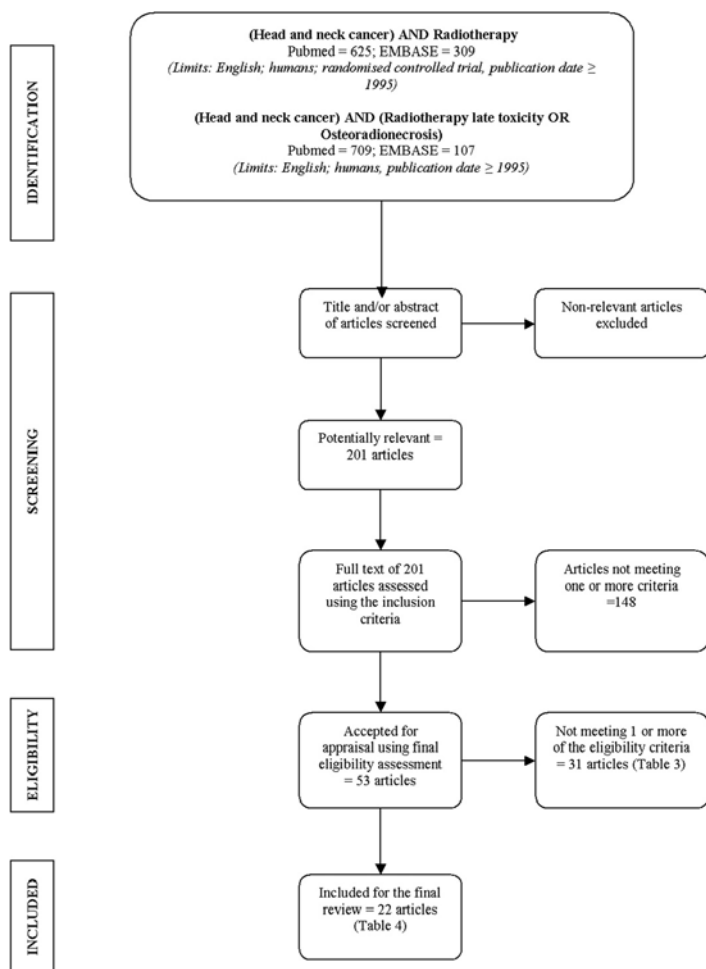
Table I. Previously reported osteoradionecrosis (ORN) incidence

<i>Author</i>	<i>Year</i>	<i>Period</i>	<i>No. of patients</i>	<i>No. of ORN</i>	<i>Percentage</i>
Watson and Scarborough ¹²	1938	1930-1937	1,819	235	12.9%
MacCombe ¹³	1962	1952-1959	251	93	37.1%
Grant and Fletcher ¹⁴	1966	1954-1962	176	66	37.5%
Bedwinek et al. ¹⁵	1976	1966-1971	381	54	14.2%
Daly et al. ¹⁶	1972	1966-1971	304	66	21.7%
Murray et al. ¹⁷	1980	1966-1975	653	138	21.1%
Morrish et al. ¹⁸	1981	1971-1977	100	22	22.0%
Withers et al. ¹⁹	1995	1976-1985	676	32	4.7%
Reuther et al. ²⁰	2003	1969-1999	830	68	8.2%

4. Aims: clarify the effects of different radiation protocols on the risk of developing ORN of the jaws in the irradiated head andneck cancer population.

II. MATERIALS AND METHODS:

1. **Objective:** using systemic literature to answer the clinical question, “What is the current risk of developing ORN of the jaws among irradiated head and neck cancer patients?”
2. **Study identification:**“head and neck cancer,” “radiotherapy,” “radiotherapy late toxicity,” and “osteoradionecrosis” as key word in Medline & Embase



3. Study selection:

Table II. Criteria for inclusion of articles in the final eligibility assessment phase

Randomized controlled trial comparing outcome of different radiotherapy treatment regimes
Patients who had undergone radiotherapy in head and neck region (excluding lymphoma, esophageal, thyroid, and tracheal tumors)
Reporting the late bone toxicity/bone necrosis/osteoradionecrosis
Sample size >20 in each arm
Excluding reirradiation
Excluding palliative treatment
Human subjects
Adult subjects

4. Type of study: randomized controlled trials (RCTs) involving RT on head and neck cancer patients with a minimum sample size of 20 patients

- i. *Participants.* Consecutive groups of adult patients who had radiation to the head and neck region excluding lymphoma, esophageal, thyroid, and tracheal tumors were eligible. Subjects who were reirradiated were

- excluded. Palliative radiation was excluded
- ii. *Intervention.* Any RT regimes performed as a curative or adjunctive therapy with surgery in the management of head and neck cancer were included
 - iii. *Outcome measures.* Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema (RTOG/EORTC), Late Effects of Normal Tissue/Somatic Objective Management Analytic (LENT/SOMA), or the National Cancer Institute Common Toxicity Criteria (NCICTC).

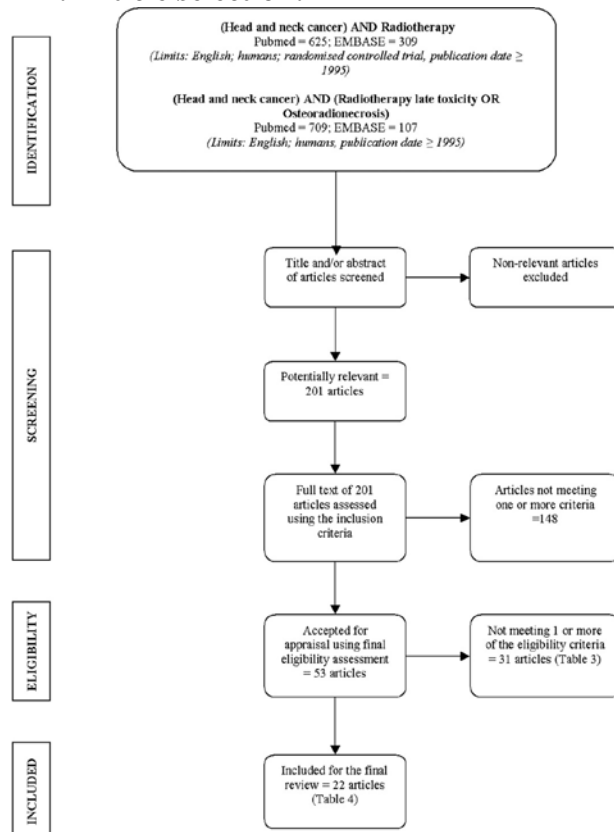
5. Eligibility assessment

- i. Actual number of cases of bone toxicity/bone necrosis/ORN reported.
- ii. Treatment regimen uniform within each arm.
- iii. Original data (no secondary analysis).
- iv. Reported follow-up of ≥ 5 years or median/mean follow-up of surviving patients ≥ 3 years.
- v. Patient recruitment beginning from 1985 onward.

6. Data collection: The data were collected in Microsoft Excel table form

III.Result:

1. Article selection:



2. Primary outcome: an incidence rate of 2%

Table IV. Articles selected for final analysis

No.	Author	Year	Follow-up	Total patients	ORN cases	Criteria of diagnosing ORN	Cancer location	Curative vs. adjunctive
1	Suwinski et al. ²¹	2008	48 mo	274	4	RTOG/EORTC	Head and neck	Adjunctive
2	Racadot et al. ²²	2008	106 mo	103	2	RTOG/EORTC	Head and neck	Adjunctive
3	Cummings et al. ²³	2007	6.9 y	331	3	RTOG/EORTC	Head and neck	Curative
4	Skladowski et al. ²⁴	2006	96 mo	90	2	RTOG/EORTC	Head and neck	Curative
5	Fallai et al. ²⁵	2006	8.35 y	112	0	Y/N	Oropharynx	Curative
6	Semrau et al. ²⁶	2006	57.3 mo	240	17	Y/N	Head and neck	Curative
7	Mendenhall et al. ²⁷	2005	38 mo	101	4	Y/N	Head and neck	Curative
8	Budach et al. ²⁸	2005	5 y	322	18	RTOG/EORTC	Head and neck	Curative
9	Huguenin et al. ²⁹	2004	39.5 mo	211	7	RTOG/EORTC	Head and neck	Curative
10	Cooper et al. ³⁰	2004	45.9 mo	409	8	RTOG/EORTC	Head and neck	Adjunctive
11	Denis et al. ³¹	2003	5.5 y	44	1	NCI-CTC and LENT/SOMA	Oropharynx	Curative
12	Corvo et al. ³²	2001	60 mo	32	0	Y/N	Head and neck	Curative
13	El-Weshi et al. ³³	2001	55 mo	34	0	RTOG/EORTC	NPC	Curative
14	Ang et al. ³⁴	2001	59 mo	182	3	RTOG/EORTC	Head and neck	Adjunctive
15	Inoue et al. ³⁵	2001	78/85 mo	51	2	Y/N	Tongue	Curative
16	Fu et al. ³⁶	2000	41.2 mo	1,029	17	RTOG/EORTC	Head and neck	Curative
17	Jeremic et al. ³⁷	2000	79 mo	130	7	RTOG/EORTC	Head and neck	Curative
18	Brizel et al. ³⁸	1998	41 mo	116	2	Y/N	Head and neck	Curative
19	Eschwege et al. ³⁹	1997	5 y	374	0	RTOG/EORTC	Head and neck	Curative
20	Dische et al. ⁴⁰	1997	6 y	918	8	Y/N	Head and neck	Curative
21	Maor et al. ⁴⁰	1995	3.5 y	135	4	RTOG/EORTC	Head and neck	Curative
22	Lee et al. ⁴¹	1995	3.38 y	504	8	RTOG/EORTC	Head and neck	Curative
Total				5,742	117	2.04%		

NPC, Nasopharyngeal carcinoma; other abbreviations as in Table III.

3. Risk of ORN for different tumor locations:

- i. 18 articles reported the outcome of RT treatment within the region of the “head and neck cancer” without subdividing to a more specific; one “nasopharyngeal carcinoma,”; 2 oropharynx and 1 tongue carcinoma
- ii. No selected articles reported the outcome of RT treatment in the sinonasal region

Table V. Osteoradionecrosis (ORN) incidence in relation to tumor site, treatment aims, radiation delivery mode, jaw involved, and dental evaluation

Variable	Articles	Total patients	ORN cases	%
Tumor sites				
Head and neck	10, 21-32, 34-41	5,708	117	2.04%
Nasopharynx	33	34	0	0%
Sinonasal	—	0	0	—
Treatment				
Adjunctive	21, 22, 30, 34	968	17	1.76%
Curative	10, 23-29, 31-33, 35-41	4,740	100	2.11%
Delivery				
EBRT	10, 21, 23-25, 28, 29, 31-33, 36-39, 41	4,521	77	1.70%
Brachytherapy	35	51	2	3.92%
IMRT/3D-CRT	—	—	—	—
Not clear	22, 26, 27, 30, 34, 40	1,170	38	3.25%
Mandible/maxilla				
Mandible	21, 22, 24, 25, 27, 31, 35	775	15	1.94%
Maxilla	—	—	—	—
Not reported	10, 23, 26, 28-30, 32-34, 36-41	4,967	102	2.05%
Dental evaluation				
Reported	22, 23, 26, 30, 31, 34, 36	2,338	51	2.18%
Not reported	10, 21, 24, 25, 27-29, 32, 33, 35, 37-41	3,404	66	1.94%

4. Risk of developing ORN when CT agents were used:Overall, 10 articles compared the outcome of RT alone to that of CRT. 5 articles reported higher incidence of ORN when CRT was used,26,28,30,31,37 3 when RT alone was used,22,29,38 whereas 2 articles reported no difference

Table VI. The use of chemoradiotherapy (CRT) and osteoradionecrosis (ORN) incidence

		ORN with CRT		ORN with RT only	
		n	%	n	%
Curative					
Fallai et al. ²⁵	2006	0/39	0%	0/73	0%
Semrau et al. ²⁶	2006	10/113	8.9%	7/127	5.5%
Budach et al. ²⁸	2005	10/164	6.1%	8/158	5.1%
Huguenin et al. ²⁹	2004	3/105	2.9%	4/106	3.8%
Denis et al. ³¹	2003	1/27	3.7%	0/17	0%
Corvo et al. ³²	2001	0/20	0%	0/12	0%
Jeremic et al. ³⁷	2000	4/65	6.2%	3/65	4.6%
Brizel et al. ³⁸	1998	0/56	0%	2/60	3.3%
Subtotal		28/589	4.75%	24/618	3.88%
Adjunctive					
Racadot et al. ²²	2008	0/52	0%	2/51	3.9%
Cooper et al. ³⁰	2004	6/201	3.0%	2/208	1.0%
Subtotal		6/253	2.37%	4/259	1.54%
Total		34/842	4.04%	29/877	3.19%

5. Risk of developing ORN in curative RT or adjunctive RT with surgery: similar risk of developing ORN was seen

Table V. Osteoradionecrosis (ORN) incidence in relation to tumor site, treatment aims, radiation delivery mode, jaw involved, and dental evaluation

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IMRT/3D-CRT	—	—	—	—
Not clear	22, 26, 27, 30, 34, 40	1,170	38	3.25%
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6. Incidence with different delivery techniques:

7. Difference in risk with different dose rates and treatment time:

Table VII. Use of altered fractionation and osteoradionecrosis (ORN) incidence

		ORN with altered fractionated RT		ORN with control	
		n	%	n	%
Hyperfractionation					
Cummings et al. ²³	2007	2/169	1.2%	1/162	0.6%
Fu et al. ²⁶	2000	7/253	2.8%	4/254	1.6%
Subtotal		9/422	2.13%	5/416	1.20%
Accelerated fractionation without total dose reduction (curative)					
Fallai et al. ²⁵	2006	0/37	0%	0/36	0%
Skladowski et al. ²⁴	2006	2/50	4.0%	0/40	0%
Fu et al. ²⁶	2000	6/522	1.2%	4/254	1.6%
Subtotal		8/609	1.31%	4/330	1.21%
Accelerated fractionation without total dose reduction (adjunctive)					
Suwinski et al. ²¹	2008	4/137	2.9%	0/137	0%
Ang et al. ²⁴	2001	1/76	1.3%	2/75	2.7%
Subtotal		5/213	2.35%	2/212	0.94%
Accelerated fractionation with total dose reduction					
Dische et al. ¹⁰	1997	2/552	0.36%	6/366	1.64%
Subtotal		2/552	0.36%	6/366	1.64%
Total		24/1796	1.34%	17/1,324	1.28%

8. Risk for the mandible and maxilla: none reported the occurrence of ORN in the maxilla within reported location.

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9. Reporting of dental evaluation: 7 articles reported

IV.DISCUSSION:

1. Criteria:

- i. spontaneously occurring ORN → extent of radiation damage to bone; high dose high rate, between 6M~2Y (Marx and Johnson)
- ii. trauma-induced ORN → the dental health, dental traumatic event, forever
- iii. present review to be _5 years of follow-up or a median/mean follow-up of _3 years. (short survival rate of head and neck cancer), 90% or more of ORN cases occur within the first 3 years after RT
- iv. ORN is defined as an area of exposed devitalized irradiated bone that fails to heal over a period of 3-6 months in the absence of local neoplastic disease

Table VIII. Late radiation bone toxicity according to the Radiation Therapy Oncology Group scoring criteria

Grade	Bone morbidity
0	None
1	Asymptomatic; no growth retardation; reduced bone density
2	Moderate pain or tenderness; growth retardation; irregular bone sclerosis
3	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis
4	Necrosis; spontaneous fracture
5	Death directly related to radiation late effects

Table IX. Late radiation mandibular morbidity according to the Late Effects of Normal Tissue/Somatic Objective Management Analytic scale*

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Mastication		Difficulty with solids	Difficulty with soft foods	
Denture use		Loose denture	Inability to use dentures	
Trismus	Noted but unmeasurable	Preventing normal eating	Difficulty eating	Inadequate oral intake
Objective				
Exposed bone		≤2 cm	>2 cm or limited sequestration	Fracture
Trismus		1-2 cm opening	0.5-1 cm opening	<0.5 cm opening
Management				
Pain	Occasional nonnarcotic	Regular nonnarcotic	Regular narcotic	Surgical intervention or resection
Exposed bone		Antibiotics	Debridement, HBO2	Resection
Trismus and mastication		Soft diet	Liquid diet, antibiotics, muscle relaxant meds.	NG tube, gastrostomy
Analytic				
Mandibular radiograph	Questionable changes or none	Osteoporosis (radioluscent) osteosclerosis (radiodense)	Sequestra	Fracture
Panograph x-ray/CT		Assessment of necrosis progression		

*Instruction: Score the 9 SOM parameters with 1-4 (score = 0 if there are no toxicities); total the score and divide by 9.

Table X. Bone toxicity according to the National Cancer Institute Common Toxicity Criteria

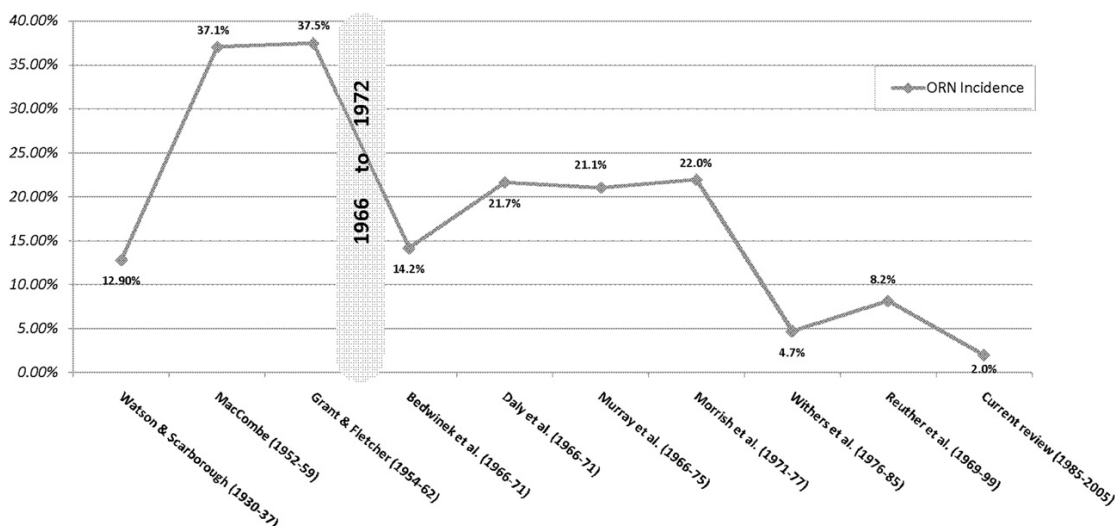
Grade	Osteonecrosis of jaw
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL; elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

ADL, Activities of daily living.

- ORN rate:** 2 out of 100 irradiated head and neck cancer patients at risk of developing ORN; 1968 Clayman find out RT dose change & systematic dental program contribute; may inclusion of all head and neck cancer sites & exclusion of reirradiation subjects

Table I. Previously reported osteoradionecrosis (ORN) incidence

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1966-1972 – The widespread use of supervoltage/megavoltage machine and the introduction of systematic dental programme pre-radiation^{16, 60-62}

3. Some that have been suggested include gender, tobacco and alcohol, tumor site or stage, invasion or proximity of tumor to bone, dental health status, treatment type (EBRT, brachytherapy, neutron beam), chemoradiotherapy, radiation dose, trauma to the bone (extraction, denture-related, cancer surgery), and dose rate/fractionation. But this review aimed on location of tumor, radiation delivery methods, curative or adjunctive therapy, different fractionation schedules, the use of CRT, and dental evaluation before RT .

4. Risk of ORN for different tumor locations:

- i. tongue, floor of mouth, alveolar ridge, or retromolar region, are sites with the highest risk of developing ORN after irradiation
- ii. sinonasal or nasopharyngeal areas present a higher risk for developing ORN in the maxilla. Reuther et al., who reviewed a series of 830 patients of oral cavity, lip, and oropharyngeal tumors, noted that only **1 out of 68 ORN cases developed in the maxilla**. But Homma et al. of **5 maxillary and 1 mandibular ORN** observed in a series of 47 sinonasal tumor patients

5. **Risk of developing ORN when CT agents were used:** Five studies reported worse ORN outcome when CRT was used compared with 3 when RT alone was used. Two other studies reported no difference. This variable outcome indicates that the addition of CT agents to RT does not appear to increase the risk of developing ORN.

6. Risk of developing ORN in curative RT or adjunctive RT with surgery:

Marx and Johnson found that among 536 ORN cases, 48 of them were considered to be directly caused by the ablative surgery before radiation, and Thorn et al. observed that 10% of ORN in their series were initiated by the tumor surgery. This review: no difference,

7. Incidence with different delivery techniques

- i. conventional
- ii. Brachytherapy occurrence rate↑
- iii. 3D-CRT or IMRT →6% ORN(for xerostomia)

8. Difference in risk with different dose rates and treatment time

- i. conventional → 1.8-2.0 Gy once daily, 5 days a week, over 4-8
- ii. hyperfraction → smaller dose but more total dose → slight increase
- iii. accelerated → shorten Tx time → total dose no change → no increase

→total dose reduction→decrease

9.risk for the mandible and maxilla: high risk of mandibule→blood supply
no article on nasopharynx or sinonasal →no maxillary ORN

10. reporting of dental evaluation: most reported ORN owing dental cause→no difference

V conclusion:

1.2/100 incidence due to OH awareness, better radiation technology, inclusion of low-risk & high-risk tumor sites, and exclusion of reirradiation patient.

2.6.88/100 in post-RT tooth extraction

3.adjunctive RT, accelerated fractionation, CRT→no definitive increase

4.hyperfractionation→ possible increased risk

5.suggest confirm tumor site, preradiotherapy dental assessment on the risk of developing ORN

題號	題目
1	本回顧中認為甚麼因素跟 ORN 沒有相關 (A) Hyperfractionation RT (B) 上顎或是下顎 (C) dental evaluation (D) Oral hygiene
答案 (C)	出處：本文獻
題號	題目
2	最讓病人困擾的 POST-RT PROBLEM (A) ORN (B) RECURRENCE (C) 以上皆是 (D) 以上皆非
答案 (C)	出處：本文獻