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MAIN ARTICLE

Cost analysis of osteoradionecrosis

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Abstract

Objective: Osteoradionecrosis is a significant complication of head and neck cancer treatment, and its most severe form (grade III) necessitates radical surgery. This study aimed to compare the cost of free-flap reconstructive surgery for grade III osteoradionecrosis and similar non-osteoradionecrosis cases in order to assess the cost burden of osteoradionecrosis treatment.

Methods: All patients who underwent free-flap reconstructive surgery for osteoradionecrosis between July 2004 and July 2010 at Auckland City Hospital (19 patients) were identified, and relevant data were collected retrospectively. These patients were matched in terms of age and sex with patients who underwent free-flap reconstructive surgery.

Results: The treatment cost was 44 per cent higher in osteoradionecrosis patients when compared to non-osteoradionecrosis patients.

Conclusion: The significant financial burden on the health system, and the growing evidence for the effectiveness of pentoxifylline, tocopherol and clodronate, should prompt us to explore this alternative treatment further.

Key words: Osteoradionecrosis; Free Tissue Flaps; Reconstructive Surgical Procedure; Costs and Cost Analysis; Therapeutics; Otolaryngology

Introduction

Osteoradionecrosis is one of the most severe late side effects of head and neck tumour treatment, in which irradiated bone becomes devitalised and exposed through overlying skin or mucosa. There are two main hypotheses that describe the underlying pathophysiology. The long-standing Marx hypothesis proposes osteoradionecrosis to be akin to a non-healing wound secondary to metabolic and homeostasis disturbance.[1,2] More recently, Delanian and Lefaix proposed that osteoradionecrosis occurs via a fibro-atrophic mechanism that involves a complex interaction between tissue ischaemia, free radical formation, endothelial dysfunction, vascular thrombosis, inflammation, fibrosis and finally tissue necrosis.[1,3]

Treatment for osteoradionecrosis remains variable, but, in general, resection and reconstruction with vascularised tissue is recommended for refractory cases.[4] Despite limited evidence to support its use, hyperbaric oxygen therapy has been widely used to treat osteoradionecrosis since the 1970s, but, in the modern era of widespread use of free-flap reconstruction, hyperbaric oxygen therapy has become increasingly unnecessary.[1,4] It has been shown that hyperbaric oxygen therapy without aggressive surgical therapy is ineffective.[1] The only randomised, placebo-controlled and blinded study of hyperbaric oxygen therapy for treating osteoradionecrosis failed to show any benefit.[5] Recent studies have shown the benefits of pentoxifylline and tocopherol use in all stages of osteoradionecrosis, this effect having been attributed to their anti-fibrotic effects.[6–8] Other therapeutic strategies including ultrasound, distraction osteogenesis, and biological agents such as BMP-1 and bFGF are not supported by clinical evidence.[1]

Currently, surgical treatment to extricate devitalised bone and free-flap reconstruction is the only useful therapy for grade III osteoradionecrosis. However, this therapy is costly and it is associated with a high morbidity.[9,10] A study from two large centres in the USA estimated the total cost of osteoradionecrosis treated by free-flap surgery, including hyperbaric oxygen therapy, surgical management, conservative management and hospital stay, to be $55 040 USD per patient.[10] This study aimed to compare the cost of surgical management of grade III osteoradionecrosis in an Australasian setting with similar surgical management in non-osteoradionecrosis patients.

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Materials and methods

Osteoradionecrosis patients

All patients who underwent free-flap reconstructive surgery for osteoradionecrosis between July 2004 and July 2010 at Auckland City Hospital were identified using the Auckland City Hospital database, and relevant data were collected. Following collection of the initial data, the administration and finance department at the Auckland District Health Board calculated the in-patient and out-patient costs (NZD). The main components of interest for an in-patient admission were: number of days in the intensive care unit; number of days on the ward; surgery, including operating theatre and implant costs; and laboratory and radiology assessments, including blood test and imaging costs. The out-patient osteoradionecrosis treatment costs included those associated with out-patient surgical and dental clinics, such as length of appointment time, staffing and hyperbaric oxygen therapy.

Non-osteoradionecrosis patients

All patients who underwent free-flap reconstructive surgery for reasons other than osteoradionecrosis between July 2004 and July 2010 at Auckland City Hospital were identified using the Auckland City Hospital database. Patients were included in the study if data regarding treatment were complete and single free-flap reconstructive surgery was performed. Age and gender matching was then performed to match these patients to the osteoradionecrosis patient cohort, and the same data points and costs were calculated.

Results

Patient data

A total of 19 patients who underwent free-flap reconstructive surgery for osteoradionecrosis were identified. Patients' ages ranged from 36 to 72 years (median, 58 years). Other patient data are presented in Table I.

Age- and gender-matched patients were found for all 19 osteoradionecrosis patients. The non-osteoradionecrosis patients' ages ranged from 35 to 75 years (median, 57 years). Other patient data are presented in Table II.

Cost

Total costs included in-patient, out-patient and hyperbaric oxygen therapy costs. A breakdown of costs and total costs for the osteoradionecrosis and non-osteoradionecrosis patients are shown in Tables III and IV. The median total costs were $123 900 NZD (£70 283 GBP) for the osteoradionecrosis patients and $86 000 NZD (£48 784 GBP) for the non-osteoradionecrosis patients (Table V).

The median cost of hyperbaric oxygen treatment in osteoradionecrosis patients was $16 500 NZD (£9360 GBP). When the hyperbaric oxygen treatment costs for osteoradionecrosis patients were excluded (total hospital cost), the median costs were $105 100 NZD (£59 619 GBP) for the osteoradionecrosis group and $86 000 NZD (£48 784 GBP) for the non-osteoradionecrosis group.

Analysis

We carried out the statistical analysis using the JMP program (SAS Institute, Cary, North Carolina, USA), and statistical significance was calculated using the Wilcoxon signed rank test.

The treatment cost for osteoradionecrosis patients (total cost) was 44 per cent higher when compared to the cost for non-osteoradionecrosis patients. This finding was statistically significant, with a p-value of 0.027 (Figure 1).

We also calculated the total hospital cost, which excluded the cost for hyperbaric oxygen treatment. This was carried out to assess the difference in the costs of surgical management between these two groups. The total hospital cost was 22 per cent higher in the osteoradionecrosis group compared to the non-osteoradionecrosis group. However, this finding was not statistically significant, with a p-value of 0.4221 (Figure 2).

Discussion

Our study reveals a substantial difference in treatment costs between the osteoradionecrosis and non-osteoradionecrosis patients, when free-flap reconstruction was utilised with or without hyperbaric oxygen.

The study also investigated cost differences when hyperbaric oxygen treatment costs were excluded. Although not statistically significant, the difference in cost is still economically significant. The insignificant p-value is likely to be because of our small study population size.

Although we did not formally analyse the reasons for increased costs in the osteoradionecrosis patients, this is likely to be a result of the higher rates of post-operative complications. More complications are expected because of poorer tissue quality associated with radiation therapy and chronic inflammation.

Surgical management, including free-flap reconstruction, is the 'gold standard' for stage III osteoradionecrosis. However, the cost of free-flap surgery for the treatment of stage III osteoradionecrosis patients is substantial and poses a significant cost burden to the New Zealand healthcare system.

A recent phase II trial by Delanian *et al.*, which used a combination of pentoxifylline, tocopherol and clodronate ('PENTOCLO'), showed this therapy to be effective in treating osteoradionecrosis.[8] That study enrolled patients with osteoradionecrosis for whom mainly hyperbaric oxygen therapy and local surgery had been ineffective. All study participants experienced complete recovery in a median of nine months, with very few reported side effects.

A randomised, placebo-controlled trial is needed to confirm the efficacy of the pentoxifylline, tocopherol and clodronate protocol; nevertheless, given the high

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TABLE I

OSTEORADIONECROSIS PATIENT INFORMATION AND CONSERVATIVE MANAGEMENT DETAILS

Pt no.	Age (y)	Gender	Osteoradionecrosis site	Pathology	TNM classification	RT dose (fractions)	Chemotherapy	Hyperbaric oxygen therapy dives (*n*)
1	58	F	L temporal bone	L parotid adenoid cystic tumour	N/A	?	None	13
2	37	F	L mandible + R mandible	SCC L oral tongue	$T_2N_0M_0$	60 Gy (30)	None	40
3	70	M	R mandible	R parotid adenocarcinoma	Poorly differentiated	60 Gy (30)	None	30
4	62	M	R mandible	SCC NPC	$T_{2b}N_1M_0$	66 Gy (33)	Cisplatin	53
5	72	M	R mandible	SCC L tongue base & lateral tongue, & tonsil	T_4N_{2b}, stage 4B	72 Gy (42)	None	50
6	60	M	Bilateral anterior mandible	SCC L lateral tongue	Pathologically staged $T_1N_{2b}M_0$	60 Gy (?)	None	?
7	58	M	R temporal bone	NPC	T_1N_2	?	None	31
8	50	F	L mandible, R mandible × 2	SCC L tonsil	T_2N_3	70 Gy (35)	Cisplatin	31
9	36	M	L lingual plate mandible, L maxilla	NPC	$T_4N_1M_X$	66 Gy (33)	Cisplatin	40
10	38	F	L mandible	SCC L tongue	$T_3N_0M_0$	?	None	30
11	66	M	L mandible	SCC R oropharynx	Clinically staged $T_2N_3M_0$	70 Gy (35)	None	95
12	45	M	L mandible	SCC R tonsil	$T_1N_{2b}M_0$	70 Gy (35)	Cisplatin, Tirapazamine®	41
13	46	M	L mandible	SCC L tonsil	T_4N_{2c}	70 Gy (35)	Cisplatin	62
14	65	M	R mandible	SCC tongue	$T_1N_3M_0$	?	None	41
15	60	F	R mandible	?	?	?	None	19
16	47	M	L mandible	SCC lower lip	Metastatic; TNM unknown	60 Gy (30)	None	31
17	56	M	L mandible	SCC floor of mouth	?	Brachytherapy with 3 iridium needles	None	40
18	58	M	L mandible	R undifferentiated NPC	T_3N_1	66 Gy (33)	None	39
19	72	M	R mandible	R parotid acinic cell carcinoma	?	66 Gy (33)	None	40

Pt no. = patient number; y = years; TNM = tumour–node–metastasis; RT = radiotherapy; F = female; L = left; N/A = not applicable; ? = unknown or missing data; R = right; SCC = squamous cell carcinoma; M = male; NPC = nasopharyngeal carcinoma

TABLE II
NON-OSTEORADIONECROSIS PATIENT INFORMATION AND CONSERVATIVE MANAGEMENT DETAILS

Pt no.	Age (y)	Gender	Pathology	TNM classification	RT dose (fractions)	Chemotherapy
1	61	F	SCC lateral tongue	$T_{4a}N_0M_0$	60 Gy (30)	Nil
2	40	F	SCC tongue	$T_3N_0M_0$	60 Gy (30)	Nil
3	65	M	SCC tongue	T_3N_0	Nil	Nil
4	67	M	SCC tongue	$T_1N_0M_0$	Nil	Nil
5	74	M	SCC tongue	T_2N_0	Nil	Nil
6	59	M	SCC hard palate & maxilla	T_4N_0	60 Gy (30)	Nil
7	57	M	SCC mandibular alveolus	Pathologically staged $T_1N_0M_0$	Nil	Nil
8	51	F	SCC floor of mouth	T_2N_{2b}	Nil	Nil
9	35	M	SCC tongue	Recurrent $T_1N_0M_0$	60 Gy (30)	Carboplatin/Taxotere® 2 cycles; capecitabine 1 cycle
10	44	F	SCC floor of mouth	$T_2N_0M_0$	Nil	Nil
11	61	M	Melanoma cheek	$T_{4a}N_2M_X$	48 Gy (20)	Nil
12	45	M	Mucoepidermoid carcinoma	T_4N_2	70 Gy (35)	Nil
13	50	M	SCC mandibular alveolus	$T_4N_{2b}M_0$	60 Gy (30)	Nil
14	68	M	SCC pinna	T_4N_0	50 Gy (25)	Nil
15	65	F	Adenoid cystic carcinoma	N/A	Nil	Nil
16	50	M	SCC tongue	$T_3N_0M_0$	60 Gy (30)	Nil
17	53	M	Chronic osteomyelitis mandible	N/A	Nil	Nil
18	57	M	SCC tongue	$T_2N_0M_0$	58 Gy (30)	Nil
19	74	M	BCC cheek	N/A	60 Gy (30)	Nil

Pt no. = patient number; y = years; TNM = tumour–node–metastasis; RT = radiotherapy; F = female; SCC = squamous cell carcinoma; M = male; N/A = not applicable; BCC = basal cell carcinoma

cost and relatively poor outcomes of other available therapies, this protocol presents an alternative therapeutic option. However, given the lack of confirmatory trials showing the efficacy of this treatment and the associated costs, Pharmac, New Zealand's pharmaceutical management agency, has not funded its use. This poses a parachute-like dilemma.[11,12] The existing treatment options for grade III osteoradionecrosis are poor, and pentoxifylline, tocopherol and clodronate therapy has considerable anecdotal and now scientific evidence[6–8] regarding its efficacy, despite no randomised controlled trial. This leaves patients suffering from osteoradionecrosis and in a situation where they face major surgery with considerable side effects, until there is good evidence confirming the efficacy of pentoxifylline, tocopherol and clodronate.

TABLE III
BREAKDOWN OF COSTS AND TOTAL COSTS FOR OSTEORADIONECROSIS PATIENTS*

Pt no.	Total in-patient cost	Total out-patient cost	Out-patient hyperbaric oxygen cost	Total cost
1	29 900	1 100	Unknown	31 000
2	76 900	29 300	19 400	125 600
3	25 300	43 800	14 500	83 600
4	120 100	43 400	241 700	405 200
5	47 500	45 300	31 100	123 900
6	49 500	12 500	Nil	62 000
7	80 100	25 100	13 800	119 000
8	76 200	54 700	19 300	150 200
9	62 900	44 700	24 900	132 500
10	81 400	60 400	14 500	156 300
11	515 100	62 800	59 200	637 100
12	54 300	33 700	19 900	107 900
13	98 400	65 400	38 600	202 400
14	53 400	19 400	12 800	85 600
15	78 900	26 200	9 200	222 400
16	46 900	36 400	14 900	98 200
17	54 700	4 300	16 900	75 900
18	54 200	20 900	16 500	91 600
19	192 700	32 800	12 600	238 100

*Rounded to nearest NZD$100. Pt no. = patient number

TABLE IV
BREAKDOWN OF COSTS AND TOTAL COSTS FOR NON-OSTEORADIONECROSIS PATIENTS*

Pt no.	Total in-patient cost	Total out-patient cost	Total cost
1	64 300	41 400	105 700
2	58 300	19 700	78 000
3	97 000	11 800	108 800
4	45 000	75 000	120 000
5	45 610	30 700	76 000
6	80 100	28 600	108 700
7	80 200	13 800	94 000
8	78 800	7 200	86 000
9	9 200	21 000	30 200
10	71 000	16 000	87 000
11	30 500	22 800	53 300
12	128 700	47 300	176 000
13	123 300	11 000	134 300
14	77 400	54 500	131 900
15	73 800	11 800	85 600
16	35 800	23 300	59 100
17	46 700	11 300	58 000
18	49 300	27 000	76 300
19	46 000	36 700	82 700

*Rounded to nearest NZD$100. Pt no. = patient number

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TABLE V
MEDIAN OF COSTS IN EACH GROUP*

Parameter	Osteoradionecrosis group (median cost (IQR))	Non-osteoradionecrosis (median cost (IQR))
In-patient cost	62 900 (49 500–81 400)	64 300 (45 610–80 100)
Out-patient cost	33 700 (20 900–45 300)	22 800 (11 800–36 700)
Total hospital cost	105 100 (72 800–141 800)	86 000 (76 300–108 800)
Hyperbaric oxygen cost	16 500 (12 800–24 900)	0
Total cost (including hyperbaric oxygen)	123 900 (85 600–202 400)	86 000 (76 300 –108 800)

*Rounded to nearest NZD$100. IQR = interquartile range

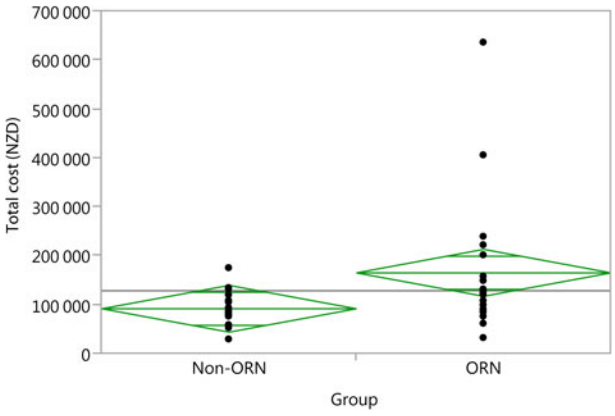

FIG. 1
Total treatment costs for osteoradionecrosis (ORN) versus non-osteoradionecrosis (non-ORN) patients.

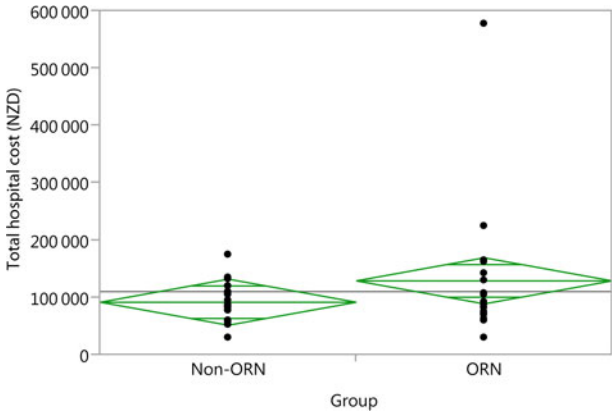

FIG. 2
Total hospital costs for osteoradionecrosis (ORN) versus non-osteoradionecrosis (non-ORN) patients, excluding the costs for hyperbaric oxygen treatment.

Interestingly, despite evidence demonstrating the inefficacy of hyperbaric oxygen therapy,[5] it is still funded by hospitals as therapy for osteoradionecrosis. This study has shown hyperbaric oxygen therapy to represent a significant cost, at a median of $16 500 NZD (£9360 GBP) per patient.

- **Treatment for osteoradionecrosis remains variable, but resection and reconstruction with vascularised tissue is generally recommended for refractory cases**
- **Despite limited supporting evidence, hyperbaric oxygen therapy is widely used to treat osteoradionecrosis**
- **Pentoxifylline, tocopherol and clodronate is a potentially effective treatment for osteoradionecrosis**
- **There is a substantial difference in treatment costs for osteoradionecrosis and non-osteoradionecrosis patients**
- **There is evidence that pentoxifylline, tocopherol and clodronate may be effective in treating this condition**

In conclusion, surgical free-flap techniques and hyperbaric oxygen for the treatment of grade III osteoradionecrosis pose a significant cost burden to the healthcare system. With this burden, and the growing evidence that the alternative possible therapy (pentoxifylline, tocopherol and clodronate) may be effective in treating this condition, we should aim to further explore the possibility of pentoxifylline, tocopherol and clodronate use.

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