

Cost analysis among oral cancer patients with and without cetuximab using administrative claims database in Japan

Takaya Kitayama¹, *Kahori Kawamura², Hideki Yoshimatsu², Takashi Doi² and Tatsuro Miyake²

¹Graduate School of Dentistry (Department of Preventive and Community Dentistry), and ²Department of Preventive and Community Dentistry, Osaka Dental University, 8-1 Kuzuhahanazono-cho, Hirakata-shi, 573-1121, Japan

*E-mail: kawamura@cc.osaka-dent.ac.jp

This study aimed to examine the medical costs associated with oral and pharyngeal cancers using a large administrative claims database in Japan. Economic evaluation is crucial for maintaining universal health coverage in Japan. We used the administrative claims database of 21,736 patients diagnosed with oral and pharyngeal cancer between April 2005 and December 2020. We calculated propensity scores based on age, sex, cancer site, lymph node metastasis, and first treatment. Using propensity score matching, we selected 195 participants from each group and compared treatment cost with and without cetuximab. The average monthly medical cost was 525,551 and 285,239 yen for the cetuximab administration and non-administration groups, respectively. When compared by sex, age, and cancer site, costs remained significantly higher in cetuximab administration group. Among the conditions during treatment, 11.8% of patients experienced hypomagnesemia due to cetuximab administration, while 7.7% exhibited common acne. Patients in the cetuximab administration group were more commonly diagnosed with cancer-related pain, oral mucositis, and difficulties with oral intake. The cost for patients with oral and pharyngeal cancer is related to patient characteristics and treatment patterns. Acknowledging the high medical expenses and need for careful attention to complications that may occur is essential. (J Osaka Dent Univ 2024; 58: 117-124)

Key words: Oral cancer; Cetuximab; Administrative claims database

INTRODUCTION

Oral and pharyngeal cancer is the 7th most prevalent cancer worldwide, accounting for approximately 710,000 new cases annually, and is the 9th leading cause of cancer-related death, responsible for 359,000 deaths worldwide each year.¹ In Japan, over 15,800 men and 6,800 women are diagnosed with oral and pharyngeal cancers annually. In 2020, the mortality was approximately 5,500 men and 2,400 women. This marks a notable increase in the proportion of individuals diagnosed with oral and pharyngeal cancers and a rising trend in mortality.² In 2015, the age-standardized (world population) death rates for oral and pharyngeal cancer per 100,000 individuals were 3.04 for men and 0.76 for

women in Japan.³ The head and neck region encompasses vital functions essential to human life, such as respiration, mastication, swallowing, phonation, and sensory functions, such as taste and hearing. Cancers of this region, including oral and pharyngeal cancers, can result in significant dental issues, limited mouth opening, and salivary secretion problems, affecting patients' quality of life (QOL), facial morphology, and social interactions.⁴

Traditionally, treatment modalities for head and neck cancers include surgery, radiation therapy, and chemotherapy, tailored according to the specific site and stage of the disease.^{5,6} Recently, treatment approaches for localized diseases and the management of recurrent and progressive conditions have made significant advancements. The

elucidation of the molecular mechanisms of cancer cells has led to promising research and the development of new treatment strategies. Successful immunotherapies have emerged for various cancers, especially for advanced melanoma, including interleukin therapies and immune checkpoint inhibitors.⁷ The ongoing investigation into immunotherapies for head and neck cancers encompasses adoptive T-cell therapy, vaccines, and immune checkpoint inhibitor proteins (e.g., anti-CTLA-1, -PD-1, -PD-L3). Potential molecular targets include inhibitors of transmembrane growth factor receptors, angiogenesis, and various signaling pathways.⁸

Cetuximab is the first human/mouse chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR) that was approved globally for the treatment of squamous cell carcinomas, which include metastatic colorectal cancer and metastatic non-small cell lung cancer.^{9, 10} For colorectal cancer, cetuximab was first approved as a second-line treatment for inoperable, advanced, or recurrent colorectal cancer in Switzerland, the US, and the EU between 2003 and 2004. It later gained approval as a first-line treatment in 2008.¹¹ In a preliminary study involving the combination of radiotherapy and cetuximab in patients with locally advanced head and neck cancer, the regimen demonstrated good tolerance, with all evaluable patients showing complete or partial regression.^{12, 13} In addition, cetuximab, used as monotherapy or in combination with cisplatin, was associated with a clinically significant tumor regression rate in patients with platinum-resistant head and neck cancer.¹⁴

Furthermore, from a health-economic perspective, the incremental cost-effectiveness ratio for adding cetuximab into standard first-line chemotherapy for patients with cancer is considered high compared to other medical interventions, making it currently non-recommendable. This underscores the need to evaluate treatment schedules with a more favorable cost-benefit ratio.^{15, 16} However, the challenges with targeted therapies include personalized cancer treatments for individual patients, evaluation of drug efficacy and toxicity, consideration of the cost-effectiveness of cancer treatments,

and management of post-treatment resistance.

Recognizing the importance of economic evaluation in maintaining universal health coverage in Japan, this study aimed to examine the cost and complication of cetuximab for the treatment of oral and pharyngeal cancer using a large administrative claims database in Japan.

MATERIALS AND METHODS

Data source

This retrospective study was based on data from the Japanese Health Administrative Database constructed by the Japan Medical Data Center Co. Ltd. (Tokyo, Japan). The Japanese Medical Data Center (JMDC) covered 16 million patients who received medical services in outpatient settings and hospitals as of November 2023. Patients diagnosed with oral and pharyngeal cancer between January 2005 and December 2020 were included in this study. The independent variables were identified using the appropriate code as listed in the International Classification of Disease, 10th version. All medical and dental claims were calculated as costs for patients with oral and pharyngeal cancers.

Study participants

We included patients diagnosed with oral and pharyngeal cancer (ICD-10 code; C00-C14). Patients diagnosed with suspected cancer were excluded. A new diagnosis was determined by the absence of cancer-related claims within 6 months after enrollment. Patients diagnosed with oral and pharyngeal cancer without treatment were excluded. Medical and dental treatments were identified using original Japanese procedure codes.

Outcomes

Each data point was linked to the claimed database file using the participants' ID numbers. We calculated medical and dental care utilization based on monthly medical expenses. Furthermore, we counted the number of all diagnosed diseases in each group and calculated the differences between treatments with and without cetuximab.

Other covariates

The patient characteristics included sex, age, working status, cancer site, metastasis and treatment. Additionally, we selected comorbid conditions such as hypertension (ICD 10 code I10-I15), diabetes mellitus (DM; ICD10 code E10-E14), liver disease (ICD10 code K70-K76), cerebrovascular disease (ICD10 code I60-I69), thyroid disorder (ICD10 code E00-E07), ischemic heart disease (ICD10 code I20-I25), heart failure (ICD10 code I50), chronic obstructive pulmonary disease (COPD; ICD10 code J43-J44), and chronic kidney disease (ICD10 code I12, N18-N19).

Propensity score matching and statistical analysis

We calculated the propensity score, defined as the conditional probability of each participant receiving cetuximab treatment. Logistic regression was used to identify several confounders, including age, sex, oral cancer site, lymph node metastasis, first treatment pattern, and comorbidities. Standardized differences were calculated to assess the balance of covariates between treatments with and without cetuximab. Covariates were considered balanced if the standardized differences were $< 10\%$.¹⁷ The propensity scores of the cetuximab and non-cetuximab groups were compared to create matched pairs (cetuximab and non-cetuximab as references) within a 0.01 caliper. In this propensity score model, a goodness of fit was secured (C-index = 0.730). Continuous measurements were analyzed using Student's *t*-test and the Wilcoxon-Mann-Whitney U test, while categorical variables were analyzed using the chi-square test. The two-sided significance level was set at $P < 0.05$. All the statistical analyses were performed using STATA/MP version 17.0 (IBM Corp., Armonk, NY, USA)

RESULTS

Table 1 presents the patient characteristics, which include sex, age, working status, cancer site, presence of metastasis, comorbidity, and initial treatment for both the cetuximab administered and non-administered groups with corresponding standard

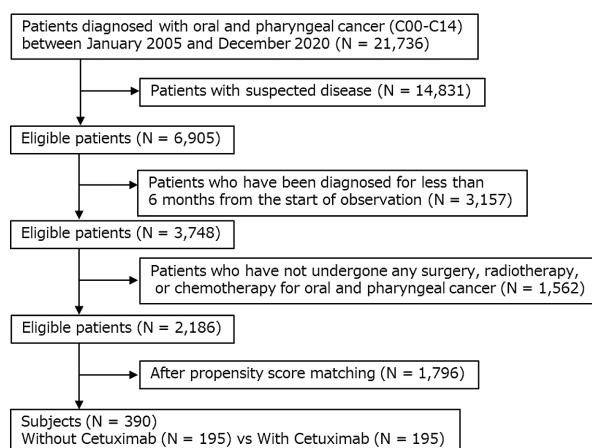


Fig. 1 Flowchart of the inclusion and exclusion.

differences. A flow diagram of this study is depicted in Fig. 1. Before propensity score matching, the cetuximab group had a mean age of 55.0 years, with 83.9% male patients, while the group without cetuximab had a mean age of 54.7 years and 74.9%, male patients. The most common cancer site was pharyngeal (N = 853, 39.0%) among the total cases. Lymph node metastasis was present in 22.0% of patients in the cetuximab non-administered group and 35.1% in the cetuximab administered group at the first diagnosis of oral and pharyngeal cancer. The prevalence of comorbidities, including hypertension, DM, liver disease, cerebral vascular disease, and ischemic heart disease, was observed among oral and pharyngeal cancers. The most common comorbidity was hypertension (N = 644; 29.5%). After propensity score matching, 390 patients with oral and pharyngeal cancer were included in this study. The standardized difference in the male-to-female ratio was not < 0.1 ; however, a balance was confirmed for the other variables.

Table 2 displays the mean monthly medical costs for patients with oral and pharyngeal cancers treated with and without cetuximab. The average monthly medical cost for the group with cetuximab administration was 525,551 yen (95% confidence interval [CI]: 231,719-338,760), while it was 285,239 yen for the group without cetuximab administration (95% CI: 481,652-569,451). Even when compared by sex, age, and site of oral and pharyn-

Table 1 Characteristics of study patients before and after propensity score matching

	Before propensity score matching					After propensity score matching				
	Without cetuximab		With cetuximab		S.d	Without cetuximab		With cetuximab		S.d
Participants	N=1,981		N=205			N=195		N=195		
Sex (N, %)					0.224					0.135
Male	1484	74.9	172	83.9		173	88.7	164	84.1	
Female	497	25.1	33	16.1		22	11.3	31	15.9	
Age (years, mean, SD)	54.7	11.1	55.0	9.9	0.029	55.4	11.1	55.3	9.6	0.01
Age-grouping (years, means, SD)										
<39	190	9.6	16	7.8	0.063	20	10.3	12	6.2	0.150
40-49	377	19.0	38	18.5	0.013	26	13.3	38	19.5	0.167
50-59	694	35.0	80	39.0	0.083	71	36.4	77	39.5	0.063
60-69	608	30.7	67	32.7	0.043	70	35.9	64	32.8	0.065
>=70	112	5.7	4	2.0	0.195	8	4.1	4	2.1	0.119
Working status (N, %)					0.145					0.049
Insured person	1638	82.7	180	87.8		175	89.7	172	88.2	
Family	343	17.3	25	12.2		20	10.3	23	11.8	
Anatomic site of the primary cancer (N, %)										
Pharynx	749	37.8	104	50.7	0.262	100	51.3	102	52.3	0.021
Tongue	724	36.5	58	28.3	0.177	57	29.2	54	27.7	0.034
Gingiva	111	5.6	17	8.3	0.106	12	6.2	14	7.2	0.041
Buccal mucosa	41	2.1	2	1.0	0.089	2	1.0	2	1.0	0.000
Salivary glands	193	9.7	15	7.3	0.087	15	7.7	15	7.7	0.000
Oral floor	64	3.2	6	2.9	0.018	6	3.1	5	2.6	0.031
Palate	39	2.0	1	0.5	0.135	1	0.5	1	0.5	0.000
Tonsil	42	2.1	2	1.0	0.093	1	0.5	2	1.0	0.059
Lip	13	0.7	0	0.0	0.115	1	0.5	0	0.0	
Other	5	0.3	0	0.0	0.071	0	0.0	0	0.0	
Metastasis (N, %)										
Lymph node	435	22.0	72	35.1	0.295	57	29.2	65	33.3	0.089
Cormorbidity (N, %)										
Diabetes mellitus	376	19.0	40	19.5	0.013	39	20.0	39	20.0	0.000
Hypertension	580	29.3	64	31.2	0.042	64	32.8	61	31.3	0.033
Cerebrovascular disease	147	7.4	18	8.8	0.050	15	7.7	16	8.2	0.019
Ischemic heart disease	119	6.0	10	4.9	0.050	9	4.6	9	4.6	0.000
Heart failure	95	4.8	12	5.9	0.047	8	4.1	11	5.6	0.072
COPD	51	2.6	2	1.0	0.121	2	1.0	2	1.0	0.000
Chronic kidney disease	41	2.1	7	3.4	0.082	8	4.1	7	3.6	0.027
Thyroid disorder	129	6.5	12	5.9	0.027	12	6.2	10	5.1	0.044
Liver disease	286	14.4	34	16.6	0.059	28	14.4	34	17.4	0.084
Treatment (N, %)										
Operation	1160	58.6	61	29.8	0.606	59	30.3	61	31.3	0.022
Neck dissection	56	2.8	6	2.9	0.006	7	3.6	6	3.1	0.029
Chemotherapy	687	34.7	119	58.0	0.482	114	58.5	112	57.4	0.021
Radiotherapy	561	28.3	63	30.7	0.053	61	31.3	62	31.8	0.011

Note. S.d: Standardized difference

Table 2 Medical costs by patient characteristics

	Without cetuximab N = 195	With cetuximab N = 195	P-value
Total (N=390)			
Mean, (95%CI)	285,239 (231,719, 338,760)	525,551 (481,652, 569,451)	<0.001
Median, (1Q, 3Q)	173,185 (85,596, 366,034)	481,761 (265,407, 728,932)	<0.001
Sex			
Male (N=337)			
Mean, (95%CI)	300,972 (241,460, 360,483)	530,138 (482,793, 577,483)	<0.001
Median, (1Q, 3Q)	179,420 (90,037, 378,433)	503,312 (290,520, 732,463)	<0.001
Female (N=53)			
Mean, (95%CI)	161,526 (98,149, 224,903)	501,283 (378,659, 623,908)	<0.001
Median, (1Q, 3Q)	111,789 (52,245, 214,995)	456,451 (218,250, 721,949)	<0.001
Age category (years)			
<=49 (N=96)			
Mean, (95%CI)	285,552 (104,665, 466,439)	606,540 (516,925, 696,155)	0.002
Median, (1Q, 3Q)	130,502 (65,170, 253,446)	566,049 (332,645, 827,309)	<0.001
50-59 (N=148)			
Mean, (95%CI)	278,246 (211,591, 344,901)	482,603 (413,372, 551,834)	<0.001
Median, (1Q, 3Q)	175,551 (85,596, 378,433)	437,617 (234,577, 721,949)	<0.001
>=60 (N=146)			
Mean, (95%CI)	291,420 (230,597, 352,243)	514,633 (440,284, 588,982)	<0.001
Median, (1Q, 3Q)	189,744 (113,481, 407,827)	486,742 (257,927, 707,906)	<0.001
Tumor site			
Pharyngeal (N=202)			
Mean, (95%CI)	327,900 (234,926, 420,873)	495,099 (433,405, 556,793)	0.003
Median, (1Q, 3Q)	189,744 (102,956, 419,919)	458,461 (236,918, 728,932)	<0.001
Tongue (N=111)			
Mean, (95%CI)	201,872 (136,706, 267,039)	599,135 (518,113, 680,158)	<0.001
Median, (1Q, 3Q)	126,197 (65,170, 210,439)	578,140 (387,177, 783,483)	<0.001
Gingiva (N=26)			
Mean, (95%CI)	319,370 (161,768, 476,971)	576,241 (373,894, 778,587)	0.044
Median, (1Q, 3Q)	266,806 (165,514, 360,853)	545,497 (325,932, 727,420)	0.040
Salivary gland (N=30)			
Mean, (95%CI)	362,503 (209,488, 515,519)	438,168 (309,813, 566,523)	0.423
Median, (1Q, 3Q)	253,446 (175,551, 650,530)	489,583 (212,161, 707,982)	0.237
Other (N=21)			
Mean, (95%CI)	186,817 (89,439, 284,194)	498,916 (236,108, 761,724)	0.017
Median, (1Q, 3Q)	132,838 (81,561, 271,740)	410,478 (245,240, 444,642)	0.008

Note. CI: Confidence Interval, 1Q, 3Q: First Quarter and Third Quarter

geal cancer, the cost remained significantly higher in cetuximab administration group.

Among the diagnosed conditions during treatment for oral and pharyngeal cancer, hypomagnesemia specific to cetuximab administration and common acne were observed in 11.8% and 7.7%

of patients, respectively. Patients in the cetuximab group were more commonly diagnosed with cancer-related pain, oral mucositis, and difficulty in oral intake during their treatment for oral and pharyngeal cancers (Table 3). A list of chemotherapeutic agents administered in combination with cetuximab

Table 3 Complications during treatment

Diagnosis code during the treatment of oral and pharyngeal cancer (N, %)	Without cetuximab N=195		With cetuximab N=195		P-value
Constipation	89	45.6	163	83.6	<0.001
Gastroesophageal reflux disease	95	48.7	143	73.3	<0.001
Cancer-related pain	83	42.6	150	76.9	<0.001
Atopic dermatitis	48	24.6	137	70.3	<0.001
Stomatitis	93	47.7	126	64.6	0.001
Xerosis	33	16.9	117	60.0	<0.001
Gastric ulcer	64	32.8	102	52.3	<0.001
Insomnia	53	27.2	101	51.8	<0.001
Chemotherapy-induced nausea and vomiting	53	27.2	101	51.8	<0.001
Oral intake difficulty	42	21.5	75	38.5	<0.001
Dysphagia	35	17.9	70	35.9	<0.001
Refractory gastroesophageal reflux disease (GERD) requiring maintenance therapy	30	15.4	68	34.9	<0.001
Radiation dermatitis	39	20.0	52	26.7	0.120
Oral candidiasis	16	8.2	24	12.3	0.182
Interstitial pneumonia	7	3.6	24	12.3	0.001
Hypomagnesemia	2	1.0	23	11.8	<0.001
Depression	15	7.7	22	11.3	0.226
Acne vulgaris	0	0.0	15	7.7	<0.001
Psoriasis	2	1.0	7	3.6	0.092

Supplementary Table 1 Chemotherapy with cetuximab

Chemotherapy with cetuximab (N, %)		
paclitaxel	86	44.1
cisplatin	52	26.7
carboplatin	37	19.0
fluorouracil	61	31.3
nivolumab	9	4.6
docetaxel	4	2.1
other	7	3.6

is presented in the Supplementary Table 1.

DISCUSSION

This study clarifies the current status of cetuximab treatment for oral and pharyngeal cancers. The strength of our study is the use of a population-based dataset that enrolled a large sample size and enabled us to trace patients even if they moved to different hospitals or clinics. Acknowledging the high medical expenses and the need for careful attention to complications that may arise during administration is essential. Cetuximab-specific adverse effects include hypomagnesemia and dermatologic manifestations such as common

acne and exacerbated psoriasis.

The major adverse effects of cetuximab treatment include skin toxicities, such as rashes, dry skin, hair growth disturbances, pruritus, and nail changes.^{18, 19} Anti-EGFR antibodies block EGFR in the nephron, inhibiting magnesium reabsorption from the distal convoluted tubule, resulting in magnesium loss from the kidneys and consequent hypomagnesemia.²⁰⁻²² Nearly all systemic agents used in cancer therapy carry the potential for hypersensitivity reactions, and the severity of these reactions range from mild flushing and itching to anaphylaxis. In rare cases, these reactions can be fatal.²³⁻²⁵ Inadequate assessment of the nature and severity of these reactions may have a negative impact on therapeutic decisions. This is especially concerning if a patient at high risk for secondary reactions is re-challenged with the drug or if aggressive treatment is discontinued in patients who might safely receive the drug. Reports have emerged regarding the incidence of adverse pulmonary reactions in patients treated with anticancer chemotherapy, including monoclonal antibodies.²⁶

A cost-effective analysis can provide valuable in-

sight into the financial implications of diseases or conditions, including medical expenses and productivity losses, as well as their impact on social and public health expenditures.²⁷ In the UK, the average treatment cost for oral cancer ranges from \$3,343 in the early stages to \$24,890 in the advanced stages. Furthermore, the costs associated with a disease can help inform priority-setting by estimating the magnitude of the problem from a financial perspective. Collecting cost-related information may encourage decision-makers to implement strategies of oral and pharyngeal cancer, especially by comparing costs across various disease stages. Systematic reviews have underscored the escalating global economic burden of oral cancer.²⁸ With an aging population and an increasing number of new oral cancer diagnoses, this knowledge is indispensable for guiding resource allocation for oral cancer care especially in healthcare settings with limited resources. The effectiveness of interventions to improve patient outcomes should be measured not only from clinical outcomes but also from an economic impact standpoint. Moreover, this analysis highlighted the cost differences between cetuximab treatment for oral and pharyngeal cancers.

This study has some limitations. First, the database we used cannot provide examination results. TNM staging was not performed in the present study. Third, the study population was limited to individuals aged < 65 years because of the Japanese medical insurance system, potentially making it non-representative of the general population with cancer. Fourth, the insurance claims database does not capture the history of tobacco and alcohol consumption.

These results provide useful information for both doctors and patients regarding the current situation of oral and pharyngeal cancer treatment with cetuximab. However, further robust research is necessary to confirm the preoperative information provided by medical providers and patients regarding treatment options for oral and pharyngeal cancer.

In conclusion, this study suggests that the cost for patients with oral and pharyngeal cancer is re-

lated to patient characteristics and treatment patterns. Acknowledging the high medical expenses and the need for careful attention to complications that may arise during administration is essential.

Acknowledgements

Ethical Approval

This study was approved by the Ethics Committee of Osaka Dental University (No.111163). The need for individual informed consent was waived because this study was a secondary analysis of an anonymized patient dataset.

Conflict of interest

There is no conflict of interests to declare.

Data Availability Statement

Data supporting the findings of this study are available from the Japan Medical Data Center. Restrictions apply to data that are not publicly available. Data are available from the authors upon reasonable request with permission from the Japan Medical Data Centre.

Funding source

This study was supported by a JSPS KAKENHI Grant-in-Aid for Young Scientists (B) (21K17204) and Osaka Dental University Research Funds (23-05).

REFERENCES

1. International Agency for Research on Cancer. Global cancer observatory. Cancer Today. Lyon: IARC. 2019, <https://gco.iarc.fr/>, [accessed November 2023].
2. CANCER STATISTICS IN JAPAN—2021. Foundation for Promotion of Cancer Research https://ganjoho.jp/public/qa_links/report/statistics/pdf/cancer_statistics_2021_data_J.pdf, [accessed November 2023].
3. Bosetti C, Carioli G, Santucci C, Bertuccio P, Gallus S, Garavello W, Negri E, La Vecchia C. Global trends in oral and pharyngeal cancer incidence and mortality. *Int J Cancer* 2020; **147**: 1040-1049. <https://doi.org/10.1002/ijc.32871>.
4. Vermaire JA, Partoredjo ASK, de Groot RJ, Brand HS, Speksnijder CM. Mastication in health-related quality of life in patients treated for oral cancer: A systematic review. *Eur J Cancer Care (Engl)* 2022; **31**: e13744. <https://doi.org/10.1111/ecc.13744>.
5. Deng H, Sambrook PJ, Logan RM. The treatment of oral cancer: an overview for dental professionals. *Aust Dent J* 2011; **56**: 244-252. <https://doi.org/10.1111/j.1834-7819.2011.01349.x>.
6. Kerawala C, Roques T, Jeannon JP, Bisase B. Oral cavity and lip cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016; **130**(Suppl 2): S83-89. <https://doi.org/10.1017/S0022215116000499>.
7. Johnson DE, Burtneess B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. *Nat Rev Dis Primers* 2020; **6**: 92. <https://doi.org/10.1038/s41572-020-00224-3>.
8. Azoury SC, Gilmore RC, Shukla V. Molecularly targeted agents and immunotherapy for the treatment of head and neck squamous cell cancer (HNSCC). *Discov Med* 2016; **21**: 507-516.

9. Wong SF. Cetuximab: an epidermal growth factor receptor monoclonal antibody for the treatment of colorectal cancer. *Clin Ther* 2005; **27**: 684-694. <https://doi.org/10.1016/j.clinthera.2005.06.003>.
10. Herbst RS, Sandler AB. Overview of the current status of human epidermal growth factor receptor inhibitors in lung cancer. *Clin Lung Cancer* 2004; **6**(Suppl 1): S7-S19. <https://doi.org/10.3816/clc.2004.s.009>.
11. Galizia G, Lieto E, De Vita F, Orditura M, Castellano P, Troiani T, Imperatore V, Ciardiello F. Cetuximab, a chimeric human mouse anti-epidermal growth factor receptor monoclonal antibody, in the treatment of human colorectal cancer. *Oncogene* 2007; **26**: 3654-2660. <https://doi.org/10.1038/sj.onc.1210381>.
12. Saleh MN, Raisch KP, Stackhouse MA, Grizzle WE, Bonner JA, Mayo MS, Kim HG, Meredith RF, Wheeler RH, Buchsbaum DJ. Combined modality therapy of A431 human epidermoid cancer using anti-EGFr antibody C225 and radiation. *Cancer Biother Radiopharm* 1999; **14**: 451-63. <https://doi.org/10.1089/cbr.1999.14.451>.
13. Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy: combining EGFR blockade with radiation. *Int J Radiat Oncol Biol Phys* 2001; **49**: 427-433. [https://doi.org/10.1016/s0360-3016\(00\)01488-7](https://doi.org/10.1016/s0360-3016(00)01488-7).
14. Vermorken JB, Mesia R, Rivera F, Remenar E, Kaweck A, Rottey S, Erfan J, Zabolotny D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; **359**: 1116-1127. doi:10.1056/NEJMoa0802656.
15. Joerger M, Matter-Walstra K, Früh M, Kühnel U, Szucs T, Pestalozzi B, Schwenkglenks M. Addition of cetuximab to first-line chemotherapy in patients with advanced non-small-cell lung cancer: a cost-utility analysis. *Ann Oncol* 2011; **22**: 567-574. <https://doi.org/10.1093/annonc/mdq431>.
16. Wu B, Yao Y, Zhang K, Ma X. RAS testing and cetuximab treatment for metastatic colorectal cancer: a cost-effectiveness analysis in a setting with limited health resources. *Oncotarget* 2017; **8**: 71164-71172. <https://doi.org/10.18632/oncotarget.17029>.
17. Cohen J. Statistical power analysis for the behavioural sciences. Hillsdale, New Jersey: Academic Press; 1988.
18. Segart S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 2005; **16**: 1425-1433. <https://doi.org/10.1093/annonc/mdi279>.
19. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer* 2006; **6**: 803-812. <https://doi.org/10.1038/nrc1970>.
20. Groenestegte WM, Thébault S, van der Wijst J, van den Berg D, Janssen R, Tejpar S, van den Heuvel LP, van Cutsem E, Hoenderop JG, Knoers NV, Bindels RJ. Impaired basolateral sorting of pro-EGF causes isolated recessive renal hypomagnesemia. *J Clin Invest* 2007; **117**: 2260-2267. <https://doi.org/10.1172/JCI31680>.
21. Schrag D, Chung KY, Flombaum C, Saltz L. Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 2005; **97**: 1221-1224. <https://doi.org/10.1093/jnci/dji242>.
22. Tejpar S, Piessevaux H, Claes K, Piront P, Hoenderop JG, Verslype C, Van Cutsem E. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 2007; **8**: 387-394. [https://doi.org/10.1016/S1470-2045\(07\)70108-0](https://doi.org/10.1016/S1470-2045(07)70108-0).
23. Lenz H-J. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007; **12**: 601-609. <https://doi.org/10.1634/theoncologist.12-5-601>.
24. Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf* 2001; **20**: 767-779. <https://doi.org/10.2165/00002018-200124100-00005>.
25. Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, Di Marco MC, Biasco G. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003; **89**: 477-481. <https://doi.org/10.1038/sj.bjc.6601155>.
26. Liu X, Hong XN, Gu YJ, Wang BY, Luo ZG, Cao J. Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphoma. *Leuk Lymphoma* 2008; **49**: 1778-1783. <https://doi.org/10.1080/10428190802270886>.
27. Byford S, Torgerson DJ, Raftery J. Economic note: cost of illness studies. *BMJ* 2000; **320**: 1335. <https://doi.org/10.1136/bmj.320.7245.1335>.
28. Ribeiro-Rotta RF, Rosa EA, Milani V, Dias NR, Masterson D, da Silva EN, Zara ALSA. The cost of oral cancer: A systematic review. *PLOS ONE* 2022; **21**: (0266346).