COST-EFFECTIVENESS ANALYSIS OF CETUXIMAB FOR THE TREATMENT OF LOCALLY ADVANCED AND DISTANT METASTATIC SQUAMOUS CELL CARCINOMA OF HEAD AND NECK IN INDIA

Final outcome report

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Executive Summary

Background: Head and neck cancer (HNC) comprises 5% of all malignancies worldwide, with head and neck squamous cell carcinoma (HNSCC) being the most common subtype. In low-middle-income countries (LMICs) and low-income countries (LICs), most (nearly 75%) HNSCCs present for treatment at a locally advanced or metastatic stage. Cetuximab is the first targeted therapy to demonstrate a significant survival benefit in patients with locally advanced HNSCC and recurrent or metastatic HNSCC. Cetuximab is a chimeric IgG1 monoclonal antibody that competitively inhibits transforming growth factor-a(TGF-a) ligand from binding to epidermal growth factor receptor (EGFR), resulting in inhibition of tumour growth, invasion and metastasis, DNA damage repair and angiogenesis. Alongside the anti-tumour effect of cetuximab as a single modality, synergistic effects are demonstrated when combined with chemotherapy and/or radiation.

Results from the pivotal randomized controlled clinical trial demonstrate significantly prolonged median locoregional control (24.4 vs. 14.9 months), progression-free survival (17.1 vs. 12.4 months) and overall survival (49.0 vs. 29.3 months) for patients treated with RT + cetuximab (RT+C) compared to RT alone. As a result, RT+C gained a place in the therapeutic spectrum in clinical practice in developed nations. Similarly, in the presence of recurrent and/or metastatic (RM) disease, not amenable for salvage surgery and/or irradiation, cetuximab plus platinum-based chemotherapy significantly improved efficacy outcomes compared with platinum-based chemotherapy alone.

Methods: A comprehensive Markov model was constructed in Microsoft Excel to assess the cost-effectiveness of use of Cetuximab in first line treatment of LA SCCHN and second line treatment of recurrent/metastatic HN cancer patients in India. In the first scenario, we estimated the health and economic outcomes of using RT alone or RT in combination with Cetuximab for the treatment of LA SCCHN patients in India. In the second scenario, we assessed the cost-effectiveness of cetuximab plus platinum-based chemotherapy against platinum-based chemotherapy alone for the treatment of recurrent or metastatic HNSCC in India. We used published literature for deriving data on clinical effectiveness of intervention and comparator arms for both the scenarios. Further, we used real world data on cost of treatments under comparison in the present study. As shown in Figure 1, the model structure comprised of three mutually exclusive health states namely progression free survival (PFS),

loco-regional recurrence (LRR), distant metastasis (DM) and death. Apart from it, two absorbing health states were also included, i.e. death from head and neck cancer in LRR and DM health states and death from natural causes in all three states namely progression free survival (PFS), loco-regional recurrence (LRR) and distant metastasis (DM). The model starts with patients at 50 years of age, the median age of diagnosis for LA SCCHN in India. All patients were assumed to enter the model in PFS state after being diagnosed with locally advanced squamous cell carcinoma of head and neck. The Markov cycle length was considered as one month, which is consistent with the KM curves provided in the published literature as well as with standard MM treatment protocol world over. Clinical, cost and effectiveness parameters were used to model the lifetime costs and consequences for a hypothetical cohort of 1000 LASCCHN and recurrent/metastatic HN cancer patients, for both intervention and comparator arms in both Scenario I and II respectively, using societal perspective. Future costs and consequences were discounted at 3% for future time preferences of cost and utility, in line with the Indian reference case methodological guidance. A lifetime horizon was considered in order to capture all costs and consequences over lifetime. We did not include the indirect cost due to productivity losses. The cost-effectiveness was assessed in terms of incremental cost effectiveness ratio (ICER) for all treatment scenarios. We have followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to report the findings.

Results: Adding cetuximab results in increased costs (ranging between ₹ 5,23,797 to 8,65,899) and health gains (ranging between 0.835-2.83 QALYs) in both scenarios when treated with platinum-based chemotherapy plus cetuximab and radiotherapy in combination with Cetuximab, respectively. Incremental costs per QALY gained was found to be ₹ 401,299 with use of RT in combination with cetuximab and ₹ 76,47,403 with use of chemotherapy in combination with cetuximab. At the currently recommended willingness to pay (WTP) threshold of one-time per capita GDP of India, we found that the combined treatment of radiotherapy + cetuximab or platinum-based chemotherapy plus cetuximab is not a cost-effective treatment option for patients with LA SCCHN and recurrent/metastatic HNSCC patients respectively in India.

Conclusion: The addition of cetuximab to radiotherapy or platinum-based chemotherapy does not provide good value for money in first-line treatment of patients with LA SCCHN and recurrent or metastatic HNSCC respectively. Our study provides an insight and supports the

evidence that Cetuximab improves survival and health-related quality of life among LA SCCHN as well as recurrent/metastatic HNSCC cancer patients, but is not cost-effective at current level of WTP threshold in India. Therefore, the present study does not recommend the inclusion of Cetuximab in oncology related health benefit packages under the world's largest health insurance scheme i.e. AB-PMJAY. The study insights can be used for clinical decision-making, guideline development, reimbursement decisions, and price negotiations. Future research may be undertaken to assess the clinical efficacy of cetuximab in subgroup of HNSCC patients with higher expression of EGFR, who are more likely to benefit from it.

Introduction

Head and neck cancer (HNC) comprises 5% of all malignancies worldwide, with head and neck squamous cell carcinoma (HNSCC) being the most common subtype [1]. HNSCCs are the seventh most common cancer by incidence accounting for 3% of global cancer mortality [2]. Approximately 650,000 new cases of HNC are diagnosed annually, resulting in 350,000 deaths [3]. In low-middle-income countries (LMICs) and low-income countries (LICs), most (nearly 75%) HNSCCs present for treatment at a locally advanced or metastatic stage [4-5]..

The standard treatments (STs) for HNC depend on the primary tumour's location and traditionally include surgery, radiotherapy (RT), and chemotherapy [6]. Treatment options for locally advanced squamous-cell carcinoma of the head and neck (LA SCCHN) include surgery and/or radiotherapy (RT), with or without concurrent chemotherapy. The main manifestations of treatment failure are loco-regional recurrences and distant metastatic disease. Management of recurrent or metastatic HNSCC that is inoperable and not amenable to salvage surgery or re-irradiation usually involves systemic chemotherapy, with platinum-based combinations being the most commonly used regimens [7]. Platinum based chemotherapeutic agents such as Cisplatin or Carboplatin either alone or in combination (with 5-fluorouracil), offer similar median overall survival (OS) of around six months, with differences only in terms of their response rates [8, 9]. Targeted agents such as cetuximab, nivolumab, or pembrolizumab offer statistically significant but small absolute improvements in overall survival [10-12].

Cetuximab is the first targeted therapy to demonstrate a significant survival benefit in patients with locally advanced HNSCC [13] and recurrent or metastatic HNSCC [14]. Cetuximab is a chimeric IgG1 monoclonal antibody that competitively inhibits transforming growth factor-a(TGF-a) ligand from binding to epidermal growth factor receptor (EGFR), resulting in inhibition of tumour growth, invasion and metastasis, DNA damage repair and angiogenesis [15-17]. Use of cetuximab has been recently adopted in platinum ineligible patients/elderly patients due to its superiority in terms of efficacy in comparison to RT alone. Alongside the anti-tumour effect of cetuximab as a single modality, synergistic effects are demonstrated when combined with chemotherapy and/or radiation [13, 18-19].

Results from the pivotal randomized controlled clinical trial demonstrate significantly prolonged median locoregional control (24.4 vs. 14.9 months), progression-free survival (17.1

vs. 12.4 months) and overall survival (49.0 vs. 29.3 months) for patients treated with RT + cetuximab (RT+C) compared to RT alone [13, 19]. As a result, RT+C gained a place in the therapeutic spectrum in clinical practice in developed nations.

Similarly, in the presence of recurrent and/or metastatic (RM) disease, not amenable for salvage surgery and/or irradiation, cetuximab plus platinum-based chemotherapy significantly improved efficacy outcomes compared with platinum-based chemotherapy alone in a randomized phase III trial in patients with recurrent or metastatic HNSCC (the EXTREME study-Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) [14]. The addition of cetuximab to platinum-based chemotherapy (cisplatin or carbo platin combined with fluorouracil) was associated with a 16% increase in response rate (P,0.001), a 2.3 month increase in progression-free survival (PFS) (P, 0.001), and a 2.7 month increase in overall survival (OS) from a median of 7.4 months to 10.1 months (P = 0.036), compared to platinum-based chemotherapy alone [14].

However, the minuscule gain in OS or progression free survival (PFS) or loco-regional control among these patients is associated with huge costs of drugs as well as treatment-related toxicities. Furthermore, in a resource-constrained nation like India, the re-allocation of government funds toward the purchase of these novel agents will entail that other patients with relatively lower costs of cancer treatment are unfairly disadvantaged. Therefore, it is important to balance financial toxicities with treatment-related toxicities.

Majority evidence on cost-effectiveness of Cetuximab originate from developed nations, so there is a need for local evidence that focus not merely on the OS gained but also account for associated costs of survival gains. Considering this gap in literature, we designed this present economic evaluation to ascertain the costs and health benefits associated with the use of Cetuximab in the first line treatment of LA SCCHN, and recurrent/metastatic head and neck cancer patients in India. In the first scenario, we compared the costs and outcomes of RT alone and in combination with Cetuximab among locally advanced head and neck cancer patients in India. In the second scenario, we assessed the cost-effectiveness of cetuximab plus platinum-based chemotherapy in recurrent or metastatic HNSCC from the perspective of Indian healthcare system. The present study provides compelling evidence on inclusion of novel drugs under health benefit packages of national flagship health insurance program – *Ayushman Bharat Pradhan Mantri Jan Arogya Yojana* (AB PM-JAY) in India.

Materials and methods

Model Structure

A comprehensive Markov model was constructed in Microsoft Excel to assess the cost-effectiveness of use of Cetuximab in first line treatment of LA SCCHN and second line treatment of recurrent/metastatic HN cancer patients in India. In the first scenario, we estimated the health and economic outcomes of using RT alone or RT in combination with Cetuximab for the treatment of LA SCCHN patients in India. In the second scenario, we assessed the cost-effectiveness of cetuximab plus platinum-based chemotherapy against platinum-based chemotherapy alone for the treatment of recurrent or metastatic HNSCC in India. We used published literature for deriving data on clinical effectiveness of intervention and comparator arms for both the scenarios [10, 13]. Further, we used real world data on cost of treatments under comparison in the present study. As shown in Figure 1, the model structure comprised of three mutually exclusive health states namely progression free survival (PFS), loco-regional recurrence (LRR), distant metastasis (DM) and death. Apart from it, two absorbing health states were also included, i.e. death from head and neck cancer in LRR and DM health states and death from natural causes in all three states namely AWP, LRR and DM.

The model starts with patients at 50 years of age, the median age of diagnosis for LA SCCHN in India [20]. All patients were assumed to enter the model in PFS state after being diagnosed with locally advanced squamous cell carcinoma of head and neck [21]. The Markov cycle length was considered as one month, which is consistent with the KM curves provided in the published literature as well as with standard MM treatment protocol world over [10, 13, 21]. Clinical, cost and effectiveness parameters were used to model the lifetime costs and consequences for a hypothetical cohort of 1000 LASCCHN and recurrent/metastatic HN cancer patients, for both intervention and comparator arms in both Scenario I and II respectively, using societal perspective. Future costs and consequences were discounted at 3% for future time preferences of cost and utility, in line with the Indian reference case methodological guidance [22]. A lifetime horizon was considered in order to capture all costs and consequences over lifetime. We did not include the indirect cost due to productivity losses. The cost-effectiveness was assessed in terms of incremental cost effectiveness ratio (ICER) for all treatment scenarios. We have followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to report the findings [23].

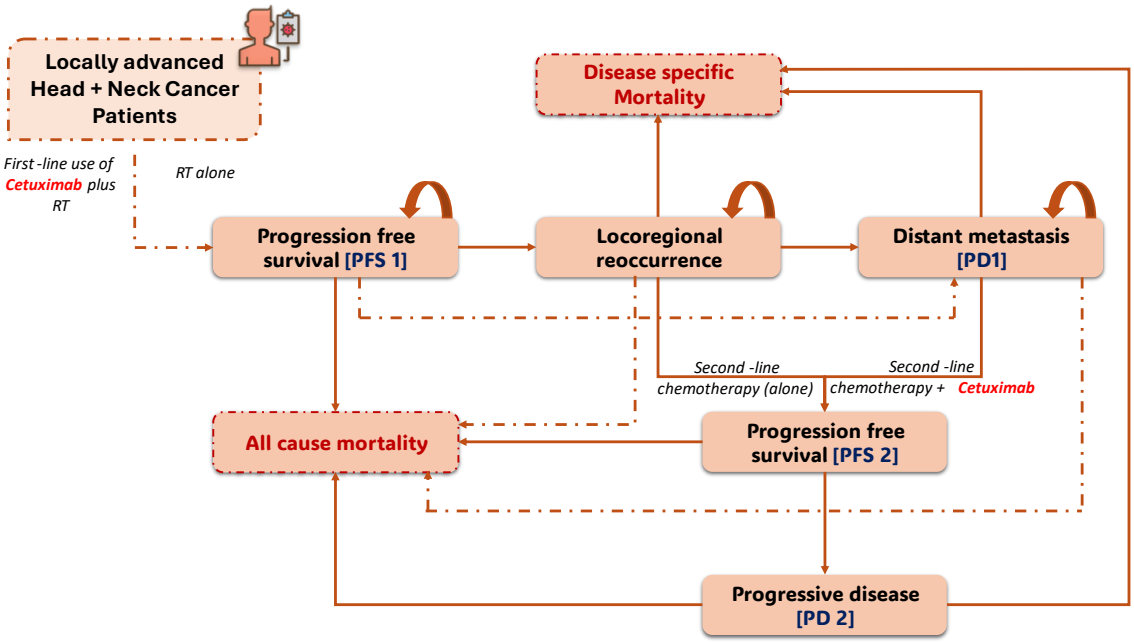

Figure 1: Model Structure

Treatment sequences

Scenario I: Two treatment arms were modelled. (1) radiotherapy alone; (2) radiotherapy plus weekly cetuximab at an initial dose of 400 mg per square meter of body surface area, followed by 250 mg per square meter weekly for the duration of radiotherapy;

Scenario II: Two treatment arms were modelled. (1) Cisplatin at a dose of 100 mg per square meter of body-surface area on day 1 plus fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks for a maximum of 6 cycles; (2) cisplatin at a dose of 100 mg per square meter of body-surface area on day 1 plus fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks for a maximum of 6 cycles plus cetuximab (at a dose of 400 mg per square meter of body surface area initially, followed by 250 mg per square meter, as a 1-hour intravenous infusion per week) for a maximum of 6 cycles.

In scenario I, all patients with LA SCCHN (PFS) were assumed to receive either RT plus Cetuximab or RT alone. In the former group i.e. RT plus cetuximab, administration of intravenous cetuximab was assumed to be initiated one week before RT at an initial loading dose of 400 mg per square meter of body surface area over a period of 120 minutes. During the administration of Injection Cetuximab, patients also received pre-medications and post-discharge medications. This was followed by RT for the maximum of 7 weeks (at a dose of 70

Gy in 35 fractions) followed by weekly infusions of Injection Cetuximab 250 mg per square meter weekly for the duration of radiotherapy (7 weeks). Further, at 6 weeks after completion of RT plus Cetuximab therapy (RT-CT), patients who had clinical progression were assumed to undergo response assessment. At 12 weeks post RT-CT, all patients in PFS health state were assumed to undergo response assessment. The response assessment was inclusive of outpatient consultation and diagnostic work up comprising Indirect Laryngoscopy (IDL), Contrast-Enhanced Computed Tomography (CECT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) scan. Further, all patients were assumed to be followed up every 3 months till one year time period, every 4 months during the second year, every six months during 3-5 years, and once a year if the patient remains in PFS health state for more than 5 years. The follow-up care was inclusive of outpatient consultation and diagnostic work up including IDL, MRI, CECT etc.

The patients who progressed to LRR health state within 2 years after the completion of RT-CT, were assumed to receive surgery (20%) or chemotherapy (70%) or RT using Intensity-modulated radiation therapy (10%). The patients who progressed to LRR health state after 2 years of the completion of RT-CT, were assumed to receive surgery (20%) or chemotherapy (60%) or RT using Intensity-modulated radiation therapy (20%). The proportions of patients in different treatment groups were elicited using expert opinion and are based on actual pattern of care in India as shown in Table 4 and Table 6. All DM patients were assumed to received chemotherapy in addition to palliative RT .

The first line chemotherapy was assumed to be given to those who had progressed for the first time i.e. patients who moved from PFS to LRR and PFS to DM. Different chemotherapeutic regimens were administered as part of first line chemotherapy as mentioned below:

1. Paclitaxel (175mg/m2) + Carboplatin (AUC 5)/ cisplatin (100mg/m2) every 3 weeks
2. Paclitaxel 175mg/m2 X 3 weekly Or Injection Docetaxel 75mg/m2 every 3 weeks
3. Injection Cisplatin 100mg/m2/ carboplatin AUC 5 + Injection 5FU 1000mg/m2 X 5 days, repeat every 3 weeks
4. Injection Pembrolizumab 200mg iv 3 weekly till PD
5. Injection Nivolumab 3mg/kg 2 weekly till PD

6. Injection. Pembrolizumab 200mg + Injection. Carboplatin AUC5 + Injection. 5FU 1000mg/m2 X 4 days for 6 cycles + continue Injection. Pembrolizumab 200mg iv 3 weekly till PD
7. Injection. cetuximab 400mg/m2, 250mg/m2+ injection. carboplatin AUC 5 + Injection. 5FU 1000mg/m2 D1-4 every 3 weeks, after 6 cycles only cetuximab till PD
8. Metronomic therapy Injection. methotrexate 40mg/m2 iv weekly till PD
9. Oral metronomic (oral MTX + celecoxib) weekly
10. Best supportive care

We applied different proportions for patients receiving different chemotherapeutic agents, based on clinical opinion. In case of patients who had progressed for the second time i.e. the patients who moved from LRR to DM, second line chemotherapy was administered. The second line chemotherapy included best supportive care (50%), metronomic therapy (20%), Injection. Carboplatin AUC5 or Injection. Paclitaxel 175 mg/m2 or Injection. Docetaxel 75mg/m2 (30%).

In the RT alone (comparator arm), RT was administered to patients with LA SCCHN patients at a dose of 70Gy in 35 fractions for the maximum of 7 weeks. The treatment protocol for LRR and DM states remained the same as described earlier.

In Scenario II, recurrent/metastatic HN cancer patients were assumed to receive either platinum-based chemotherapy i.e. Cisplatin at a dose of 100 mg per square meter of body-surface area on day 1 plus fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks for a maximum of 6 cycles, or the platinum-based chemotherapy at a similar dose of cisplatin at a dose of 100 mg per square meter of body-surface area on day 1 plus fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks for a maximum of 6 cycles plus cetuximab (at a dose of 400 mg per square meter of body surface area initially, followed by 250 mg per square meter, as a 1-hour intravenous infusion per week) for a. Further, patients with stable disease after receiving chemotherapy plus cetuximab in scenario II were assumed to receive weekly cetuximab at a dose of 250mg per metre square until disease progression [10, 13]. During the progressive disease health state, all patients were assumed to receive best supportive care (50%), metronomic therapy (20%), Injection Paclitaxel 175 mg/m2 or Injection Docetaxel 75mg/m2 (30%).

Valuation of consequences

A literature review was conducted to identify relevant clinical evidence on effectiveness of RT alone and RT in combination with Cetuximab and platinum-based chemotherapy with Cetuximab and chemotherapy alone for the treatment of LA SCCHN and recurrent/metastatic HN cancer respectively. In the absence of clinical effectiveness data from India, we used data from Bonner 2006 trial for the Scenario I and EXTREME trial for the scenario II [10,13]. The PFS Kaplan Meir (KM) curves obtained via published literature for each drug combination were digitized using Engauge (version 4.1) software [24] and individual patient data (IPD) ere pooled (S1 appendix, Figure-1). After pooling PFS data, parametric curves were fitted assuming the following distributions: exponential, Weibull, log-logistic, log-normal, generalized gamma and gompertz. The best fitting distribution was chosen based on statistical information criteria, visual inspection of the curve and clinical plausibility [25]. The survival functions were used to estimate monthly transition probabilities from the initial PFS state to LRR health state as shown in Table 1 [10, 13]. Similarly, monthly probabilities to be in PFS state were used for Scenario II as shown in Table 2. The KM curves and fitted parametric curves for each treatment arm for PFS are given in supplementary appendix I (Figure 1 and 2).

Measurement of QALYs

The outcomes were assessed in terms of life-years (LYs) and quality-adjusted life years (QALYs). In order to mimic the real-world scenario, we derived mortality rates for LRR and DM health states from an Indian study reporting five-year survival rates among oropharynx, hypopharynx and larynx cancer patients. [26]. Age specific all-cause mortality rates were obtained from the Indian Sample Registration System (SRS) lifetables [27]. The rates were converted to transition probabilities using standard methods [28].

Stage wise utility scores were obtained from the nationally representative study (CaDCQoL) being undertaken to develop a database of costs and health-related quality of life (HRQoL) [20, 29]. Primary data were collected from 1,113 head and neck cancer patients selected from 6 Indian states, who were interviewed using EQ-5D-5L tool to measure the HRQoL (Table 1 and Table 2). The Indian tariff values were used to calculate the index utility score [30].

Cost of treatment of LA SCCHN and Recurrent/Metastatic HN cancer

The comparative cost-effectiveness was assessed in terms of incremental cost per QALY gained i.e. incremental cost-effectiveness ratio (ICER). The costs were estimated from societal

perspective for all treatment arms. In Scenario I, the cost of treatment in the PFS state included the cost of diagnostic such as direct laryngoscopy and biopsy, MRI, CECT, , PET scan, Chest X-ray; consultation for dental evaluation, Nutrition/speech; cost of drug administration, cost of RT, management of AEs (grades 3-4), and the cost of routine follow-up. Routine follow-up cost included cost per outpatient consultation in oncology department, cost of routine laboratory investigations and diagnostic tests (Table 3). The cost of treatment in LRR health state was inclusive of cost of diagnostics, cost of administration of first-line and second-line chemotherapeutic agents, surgery, and RT. In DM state, the cost of outpatient consultation, routine laboratory and diagnostic tests, drug acquisition cost for first line and second-line chemotherapy and maintenance therapy were included. It was assumed that the maintenance therapy would be given to the patients in PD state till death. The costs were applied separately in each cycle using the treatment protocol obtained from the subject experts and standard treatment guidelines as per Indian Council of Medical Research (ICMR) consensus document on the management of MM [21].

We have used reimbursement rates under publicly financed national insurance program to elicit the societal cost of RT and chemotherapeutic regimens [31]. The reimbursement rates are inclusive of chemotherapeutic agents, recurring investigations, day care / inpatient charges, supportive care and professional charges. Supportive care per cycle, such as use of antiemetics, pre-medication, post chemo prophylaxis etc. are all included in the package cost. In addition to this, we included direct non-medical expenditure (including travelling, boarding/lodging, food, informal payments etc.) using primary data collected based on the CADCQoL database [21, 32].

However, for cetuximab and certain other chemotherapeutic agents like Injection Pembrolizumab, Injection Nivolumab etc. which are not included under any publicly financed health insurance scheme, we have used market prices. [Table 3 and Table 5]. To account for the cost of diagnostic services, we used the provider payment rates under the Central Government Health Scheme (CGHS) – a publicly financed national insurance scheme [33]. All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 76.2 [34].

Cost of management of adverse events

We have used proportions for commonly occurring grade 3-4 adverse events in both scenarios. The treatment costs were applied if the package of the corresponding treatment was not covered under AB PM-JAY scheme. The percentage of commonly reported adverse events considered in both scenarios are depicted in Table 8 and Table 9.

Sensitivity analyses

Univariate sensitivity analysis was also undertaken to assess the effect that each parameter has on ICER. A multivariable probabilistic sensitivity analysis (PSA) was undertaken to estimate the effect of joint parameter uncertainty [35]. Under PSA, all cost parameters were assigned gamma distribution, while utility values and probabilities/proportions were assigned beta distribution. The value of standard error (SE) was used to create a distribution around the point estimate of a parameter. In cases where SE was not reported, a variation of 50% and 10% on either side of the base value was used for cost and clinical parameters respectively. The median value of ICER along the 2.5th and 97.5th percentile was calculated using 999 Monte Carlo simulations. The per capita GDP of India of ₹ 1,71,498 (US$2,182) for the year 2023-24 was used to compare ICERs to make recommendations about cost-effectiveness [36].

Ethical approval

Ethical approval was obtained from Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research, India with reference number IEC-03/20202-1565.

Table 1: Model input parameters for assessing the effectiveness of RT alone and RT plus Cetuximab (Scenario I)

Transition probabilities to move from PFS to LRR		
Time period	**RT alone**	**RT plus cetuximab**
1	0.031802472	0.016148228
2	0.039485614	0.022410153
3	0.042444385	0.025759262
4	0.043389426	0.027568254
5	0.043381799	0.028512954
6	0.042896921	0.028946297
7	0.042169082	0.029065192
8	0.041321586	0.028985627
9	0.040422275	0.028778929
10	0.039509518	0.028490483
11	0.038605266	0.028149952
12	0.037722	0.027777141
13	0.036866588	0.027385482
14	0.036042511	0.026984196
15	0.035251188	0.026579657
16	0.034492781	0.026176284
17	0.033766687	0.025777134
18	0.033071858	0.025384302
19	0.032406995	0.0249992
20	0.031770675	0.02462275
21	0.031161434	0.024255519
22	0.030577812	0.023897821
23	0.03001839	0.023549783
24	0.029481804	0.023211401
25	0.028966759	0.022882573
26	0.028472028	0.022563133
27	0.027996463	0.022252865
28	0.027538981	0.021951524
29	0.027098575	0.021658842
30	0.026674299	0.021374542
31	0.026265273	0.02109834
32	0.025870676	0.020829952
33	0.025489739	0.020569094
34	0.025121747	0.020315489
35	0.02476603	0.020068867
36	0.024421965	0.019828965
37	0.024088968	0.019595528
38	0.023766492	0.01936831
39	0.023454027	0.019147075
40	0.023151093	0.018931598
41	0.022857243	0.018721659
42	0.022572054	0.018517051
43	0.022295132	0.018317575

44	0.022026105	0.01812304
45	0.021764624	0.017933263
46	0.021510359	0.01774807
47	0.021263002	0.017567295
48	0.021022259	0.01739078
49	0.020787855	0.017218371
50	0.020559529	0.017049925
51	0.020337036	0.016885301
52	0.020120143	0.016724369
53	0.01990863	0.016567001
54	0.019702288	0.016413076
55	0.019500918	0.016262479
56	0.019304335	0.016115098
57	0.019112358	0.015970828
58	0.01892482	0.015829568
59	0.018741559	0.01569122
60	0.018562423	0.015555692
61	0.018387265	0.015422893
62	0.018215948	0.01529274
63	0.018048339	0.01516515
64	0.017884312	0.015040044
65	0.017723747	0.014917347
66	0.017566529	0.014796988
67	0.017412548	0.014678896
68	0.0172617	0.014563005
69	0.017113885	0.014449251
70	0.016969007	0.014337572
71	0.016826974	0.014227909
72	0.016687698	0.014120206
73	0.016551095	0.014014407
74	0.016417085	0.013910459
75	0.01628559	0.013808312
76	0.016156535	0.013707918
77	0.01602985	0.013609228
78	0.015905466	0.013512197
79	0.015783318	0.013416782
80	0.015663342	0.013322941
81	0.015545476	0.013230632
82	0.015429664	0.013139816
83	0.015315849	0.013050456
84	0.015203975	0.012962515
85	0.015093992	0.012875957
86	0.014985849	0.012790747
87	0.014879498	0.012706854
88	0.014774891	0.012624245
89	0.014671984	0.012542889
90	0.014570733	0.012462756

91	0.014471097	0.012383817
92	0.014373034	0.012306045
93	0.014276506	0.012229411
94	0.014181475	0.012153891
95	0.014087904	0.012079457
Probability to die in progressive disease state (constant)		
	0.019649694	0.016702240
Utility scores for stage 3 and 4 head and neck cancer		
Progression free survival	0.603	0.603
LRR or Distant metastasis	0.458	0.458

Table 2: Model input parameters for assessing the effectiveness of Platinum-based chemotherapy alone and Platinum-based chemotherapy plus Cetuximab (Scenario II)

	Probability to in PFS state	
Time period	**Chemotherapy alone**	**Chemotherapy plus Cetuximab**
1	0.807975785	0.859137319
2	0.744840918	0.84120243
3	0.727875843	0.840834093
4	0.734194441	0.845452652
5	0.749692157	0.851480333
6	0.76767254	0.857714874
7	0.785324051	0.8637235
8	0.801606286	0.869357308
9	0.816239859	0.874580076
10	0.829255613	0.879401326
11	0.84079826	0.883848297
12	0.851042536	0.887953766
13	0.860158869	0.891750718
14	0.868300787	0.8952701
15	0.87560171	0.898540017
16	0.882175633	0.90158557
17	0.888119223	0.904428993
18	0.893514256	0.907089914
19	0.898429946	0.909585638
20	0.902925004	0.911931433
21	0.907049393	0.914140789
22	0.91084579	0.916225654
23	0.914350794	0.918196628
24	0.917595923	0.920063149
25	0.920608431	0.921833638
26	0.923411985	0.923515628
27	0.926027213	0.92511588
28	0.92847217	0.926640477
29	0.930762717	0.928094902
30	0.932912833	0.929484118
31	0.934934887	0.930812619
32	0.936839855	0.932084491

33	0.938637511	0.933303454
34	0.940336582	0.934472902
35	0.941944884	0.935595942
36	0.943469438	0.936675418
37	0.944916564	0.937713942
38	0.946291969	0.938713918
39	0.947600816	0.939677561
40	0.948847788	0.940606914
41	0.950037143	0.941503868
42	0.951172759	0.942370174
43	0.952258176	0.943207455
44	0.953296632	0.94401722
45	0.954291094	0.944800871
46	0.955244285	0.945559716
47	0.95615871	0.946294974
48	0.957036675	0.947007783
49	0.957880308	0.947699207
50	0.958691578	0.948370245
51	0.959472302	0.949021829
52	0.960224168	0.949654836
53	0.96094874	0.95027009
54	0.961647474	0.950868364
55	0.962321722	0.951450387
56	0.962972744	0.952016846
57	0.963601718	0.952568389
58	0.96420974	0.953105625
59	0.964797838	0.953629133
60	0.965366972	0.954139459
61	0.965918042	0.954637118
62	0.966451893	0.955122601
63	0.966969318	0.95559637
64	0.967471061	0.956058866
65	0.967957822	0.956510506
66	0.968430262	0.956951687
67	0.968889001	0.957382787
68	0.969334627	0.957804163
69	0.969767691	0.958216157
70	0.970188717	0.958619095
71	0.970598199	0.959013286
72	0.970996605	0.959399026
73	0.971384376	0.959776598
74	0.971761933	0.96014627
75	0.972129673	0.9605083
76	0.972487973	0.960862935
77	0.972837191	0.961210408
78	0.973177669	0.961550947
79	0.973509729	0.961884765
80	0.97383368	0.962212071
81	0.974149814	0.962533061
82	0.97445841	0.962847926
83	0.974759736	0.963156847

84	0.975054043	0.963459999
85	0.975341575	0.963757551
86	0.975622562	0.964049663
87	0.975897226	0.964336491
88	0.976165776	0.964618182
89	0.976428414	0.964894881
90	0.976685334	0.965166726
91	0.976936719	0.965433848
92	0.977182747	0.965696376
93	0.977423587	0.965954433
94	0.977659401	0.966208138
95	0.977890345	0.966457604
Probability to die in progressive disease state (constant)		
	0.007775326	0.005702714
Utility scores for stage 3 and 4 head and neck cancer		
Progression free survival	0.603	0.603
LRR or Distant metastasis	0.458	0.458

Table 3: Cost parameters for assessing the cost-effectiveness of Radiotherapy with Concomitant Cetuximab and Radiotherapy alone

Treatment Parameters	Cost (NABH)	Source
Diagnostics and Laboratory investigations		
Direct Laryngoscopy & Biopsy	5750	CGHS
Contrast-enhanced computed tomography (CECT) (BOS to T4)	2200	CGHS
Magnetic resonance imaging (MRI) with Contrast	5750	CGHS
Positron emission tomography (PET) scan	23607	CGHS
Chest X-ray	70	CGHS
Contrast-enhanced computed tomography-Chest	2000	CGHS
Dental Evaluation & Tooth Extraction	92	CGHS
Nutrition/ speech/ swallowing consultation	350	CGHS
Complete blood count	155	CGHS
Renal function tests	259	CGHS
Liver function tests	259	CGHS
Serum electrolytes	253	CGHS
Fasting blood sugar	28	CGHS
Chemotherapy		
Injection Cetuximab 400mg/m2 (per 100 mg)	73000	RMSC
Cost per day-care visit	1038	Published literature
Pre-medications		
Injection Avil	22	MRP
Injection Graniset 3mg	70	MRP
Injection Dexona 16 mg	12	MRP
Injection Rantac 50mg	6	MRP
Post-Discharge medications		

Tab Pantop 40mg	63.6	RMSC
Tab Dolo 650mg	30	MRP
Tab Emeset 4mg	40	MRP
Tab Loperamide	25	MRP
Radiotherapy RT (70 Gy/ 35 fractions/ 7 weeks)		
IMRT	70000	HBP 2022
3DCRT	21000	HBP 2022
2DRT	11000	HBP 2022
Surgery cost (neck dissection/ local Sx)	26579	HBP 2022
First line chemotherapy		
Paclitaxel (175mg/m2) + Carboplatin (AUC 5)/ cisplatin (100mg/m2)	14500	HBP 2022
Paclitaxel 175mg/m2	11800	HBP 2022
Injection Cisplatin 100mg/m2/ carboplatin AUC 5 + Injection 5FU 1000mg/m2 X 5 days	14100	HBP 2022
Injection Pembrolizumab 200mg IV	150000	MRP
Injection Nivolumab 3mg/kg 2 weekly till PD	70000	MRP
Injection Pembrolizumab 200mg + Injection Carboplatin AUC5 + Injection 5FU 1000mg/m2	Pembrolizumab = 150000 Package = 14500	MRP+ HBP 2022
Injection cetuximab 400mg/m2D1, 250mg/m2 D2,3 + injection carboplatin AUC 5 D1 + Injection 5FU 1000mg/m2 D1-4	Cetuximab -= 73000 + Package = 13900	RMSC + HBP 2022
Metronomic therapy Injection methotrexate 40mg/m2 IV	1000	MRP
Best supportive care	8500	
Second line chemotherapy		
BSC	8500	HBP 2022
Metronomic		
Injection Carboplatin AUC 5/ Injection Paclitaxel 175mg/m2/ Injection Docetaxel 75mg/m2	14500	HBP 2022

Table 4: Proportions used for assessing the cost-effectiveness of Radiotherapy with Concomitant Cetuximab and Radiotherapy alone

Parameter	Percentage
Diagnostics and Laboratory investigations	
Contrast-enhanced computed tomography (CECT) (BOS to T4)	80%
Magnetic resonance imaging (MRI) with Contrast	15%
Positron emission tomography (PET) scan	5%
Chest X-Ray	60%
CECT Chest	40%
Ryles Tube Insertion	50%
Intensity-modulated Radiation therapy	60%
3D- Conformal radiation therapy (3DCRT)	20%
2D Radiation therapy	20%

Response assessment	
CECT	60%
MRI	10%
PET Scan	30%
For patients who progressed to LRR< 2 years	
Surgery	20%
Chemotherapy	70%
Radiation therapy (RT)	10%
For patients who progressed to LRR< 2 years	
Surgery	20%
Chemotherapy	60%
RT	20%
Patients in Distant Metastasis: First line chemotherapy	
Chemotherapy	100%
Palliative RT	20%
Paclitaxel (175mg/m2) + Carboplatin (AUC 5)/ cisplatin (100mg/m2)	25%
Paclitaxel 175mg/m2 X 3 weekly Or Injection Docetaxel 75mg/m2 x 3weekly	20%
Injection Cisplatin 100mg/m2/ carboplatin AUC 5 + Injection 5FU 1000mg/m2	25%
Pem + Niv + PemCF + Cetuximab	5%
Iv + oral metronomic	15%
Best supportive care	10%
Second line therapy: Second line chemotherapy	
Best supportive care	50%
Metronomic	20%
Injection Carboplatin AUC 5/ Injection Paclitaxel 175mg/m2/ Injection Docetaxel 75mg/m2	30%

Table 5: Cost parameters used for assessing the cost-effectiveness of Platinum-based chemotherapy combined with Cetuximab and Platinum-based chemotherapy alone

Treatment Parameters	Cost (NABH)	Source
Biopsy Fine needle aspiration cytology	720	High-end diagnostics list HBP 2022
Complete blood count	155	CGHS
Renal function tests	259	CGHS
Liver function tests	259	CGHS
Fasting blood sugar	28	CGHS
Serum electrolytes	253	CGHS
Contrast-enhanced computed tomography	2200	CGHS
Positron emission tomography (PET) scan	23607	CGHS
Magnetic resonance imaging (MRI) with Contrast	5750	CGHS
Injection Cisplatin 100mg/m2 D1	5600	HBP 2022
Injection Carboplatin AUC 5 D1	7000	HBP 2022
Injection 5FU 1000mg/m2 x D1-4	100	MRP
Injection Cetuximab 400mg/m2 week 1	73000	RMSC
Injection Paclitaxel 175mg/m2	11800	HBP 2022

Injection Docetaxel 75mg/m2	8500	HBP 2022
Injection Methotrexate 40mg/m2 iv	1000	MRP
Best supportive care	8500	HBP 2022

Table 6: Proportions used for assessing the assessing the cost-effectiveness of Platinum-based chemotherapy combined with Cetuximab and Platinum-based chemotherapy alone

Parameters	Percentage
Contrast-enhanced computed tomography	75%
Positron emission tomography (PET) scan	20%
Magnetic resonance imaging (MRI) with Contrast	5%
Injection Paclitaxel 175mg/m2	30%
Injection Docetaxel 75mg/m2	30%
Injection Methotrexate 40mg/m2 iv 2 weekly	20%
Oral metronomic	20%
Best supportive care	50%

Table 7: Cost parameters for assessing the cost of management of treatment associated adverse events

Treatment Parameters	Price	Source
Clindamycin 1% gel	60	MRP
Erythromycin 3% gel	22	MRP
Metronidazole 0.75% -1% gel	62	MRP
	60	MRP
	22	MRP
	62	MRP
Tab minocycline 100mg	39.6	MRP
Tab Doxycycline 100mg	9	MRP
Tab Prednisolone 0.5mg/kg	0.9	MRP
	60	MRP
	22	MRP
	62	MRP
Tab Retinoids Isotretinoin 0.5mg/kg	48	MRP
	0.9	MRP
Injection Augmentin 1.2 gm	135.47	MRP
Injection Avil 25mg	23.38	MRP
Injection hydrocortisone 100mg	31.7	MRP
Tab paracetamol 650mg PO	1.98	MRP
Injection Rantac 50 mg	5.30	MRP
Betadine mouth wash *(50 ml)*	88	MRP
Syrp Mucain gel *(200 ml)*	213.8	MRP
Oint Mucopain (15 g)	76	MRP
Tab Tramadol 50mg	7	MRP
Betnesol oral drops *(10 ml)*	22.4	MRP
Tab fluconazole 150mg OD	18.28	MRP
Gentian Voilet *(30 ml)*	30.60	MRP
Oint Radiogen/ Radiocare	2940	MRP
Oral spray Drimouth	164	MRP

Tab megestrol 40mg	25.43	MRP
Tab PCM 650 mg QID (25%)	1.98	MRP
Tab Tramadol 50 mg QID (50%)	7	MRP
Tab tramadol + Tab PCM (20%)	10.9	MRP
Tab morphine 10mg 4hrly (5%)	62	MRP
Tab emeset 8mg	9.132	MRP
Syrp Looz 3 *(150 ml)*	238.5	MRP
Tab loperamide	2.2	MRP
Tab Pantocid 40mg	10.63	MRP
Tab Omez 20 mg	2.88	MRP
Tab Fluconazole 150mg	11.9	MRP
Tab metrogyl 400mg	1.493	MRP
Cap Augmentin 625mg	18	MRP
Tab Levoflox 750mg	12.24	MRP
Injection GCSF 300mcg	1504	MRP
Iron folic acid tablet	2.5	MRP
	1504	MRP
2 amp KCL + 500cc NS (indoor)	17.6	MRP
	27.28	MRP
Syrp Potklor *(200 ml)*	59	MRP
Nebulization with duolin 3ml respule	110	MRP
	21.92	MRP

Table 8: Common adverse events considered for cost-effectiveness analysis of RT alone and RT combined with Cetuximab

Adverse events	Grades	RT alone	RT plus Cetuximab
Rashes	Grade 1-2	9%	70%
	Grade 3	1%	17%
	Grade 4	1%	17%
Hypersensitivity reactions	Grade 3-4	2%	3%
Mucositis	Grade 3-4	52%	56%
Dysphagia	Grade 3-4	30%	26%
Dermatitis	Grade 3-4	18%	23%
Xerostomia	Grade 3-4	3%	5%
Weight loss	Grade 3-4	7%	11%
Pain	Grade 3-4	7%	6%
Nausea/Vomitting	Grade 3-4	6%	4%
Constipation	Grade 3-4	5%	5%
Diarrhoea	Grade 3-4	1%	2%
Dyspepsia	Grade 3-4	1%	0%
Infection	Grade 3-4	1%	1%
Anaemia	Grade 1,2	7%	2%
Anaemia	Grade 2-4	6%	1%

Table 9: Common adverse events considered for cost-effectiveness analysis of platinum-based chemotherapy alone and chemotherapy combined with Cetuximab

Adverse events	Grades	Chemo plus cetuximab	Chemo alone
Skin reactions (Rashes)	Grade 3-4	**9%**	**0.50%**
Anorexia (Weight loss)	Grade 3-4	6%	1.50%
Nausea/Vomiting	Grade 3-4	5%	3%
Febrile Neutropenia	Grade 3-4	6%	7%
Neutropenia without fever	Grade 2- 4	26%	31%
Anaemia	Grade 3,4	14%	20%
Thrombocytopenia	Grade 3-4	11%	12%
Leukopenia	Grade 3-4	11%	11%
Hypokalaemia	Grade 3-4	8%	5.50%
Dyspnoea	Grade 3-4	5%	10%

Results

We estimated that a patient having LA SCCHN incurs a lifetime cost of ₹ 7,21,969 when treated with radiotherapy alone as compared to ₹ 8,65,899 when treated with radiotherapy in combination with Cetuximab. [Table 10] The lifetime cost incurred by a recurrent/metastatic HN cancer patient was estimated to be ₹ 1,91,942 when treated with platinum-based chemotherapy as against ₹ 5,23,797 when treated with platinum-based chemotherapy in combination with Cetuximab. [Table 11]

A patient having LASCCHN when treated with radiotherapy plus cetuximab was found to have an overall mean survival of 5.26 years as compared to 4.70 years when treated with radiotherapy alone. After factoring in the quality of life, this would translate into 2.83 (RT-CT) and 2.468 (RT alone) QALYs respectively. [Table 10]

However, recurrent/metastatic HN cancer patient when treated with platinum-based chemotherapy plus cetuximab was found to yield marginally better health outcomes as compared to chemotherapy alone (1.64 LYs Vs 01.61 QALYs). After factoring in the quality of life, this would translate into 0.835 (RT-CT) and 0.792 (RT alone) QALYs respectively. [Table 11]

Cost-effectiveness

In Scenario I, RT alone arm has lesser cost and health benefits as compared to RT plus cetuximab. The incremental cost incurred per LY gained with use of RT in combination with

cetuximab was estimated as ₹ 2,56,635. The incremental cost incurred per QALY gained with use of RT in combination with cetuximab was estimated as ₹ 401,299.

The ICERs of RT plus cetuximab arm [₹ 401,299)] and Platinum-based chemotherapy plus cetuximab arm [₹ 76,47,403] are 2.3 and 44.5 times the per-capita GDP of India respectively. Hence, Cetuximab is not cost-effective at the currently recommended willingness to pay (WTP) threshold of per capita GDP. [Table 10] [Table 11]

Table 10: Undiscounted costs, outcomes and cost- effectiveness of Radiotherapy alone and Radiotherapy combined with Cetuximab for treatment of locally advanced squamous cell carcinoma of head and neck cancer in India

Undiscounted Results								
Scenario 1	**Undiscounted LYs**	**Undiscounted QALYs**	**Undiscounted Costs**	**Incremental effects (LYs)**	**Incremental effects (QALYs)**	**Incremental costs**	**ICER (LY)**	**ICER (QALY)**
RT plus Cetuximab	5.809	3.125	903309.6336	0.651	0.412	146095	**2,24,425**	**3,54,715**
RT alone	5.158	2.713	757214.2168					
Discounted Results								
	Discounted LYs	**Discounted QALYs**	**Discounted Costs**	**Incremental effects (LYs)**	**Incremental effects (QALYs)**	**Incremental costs**	**ICER (LY)**	**ICER (QALY)**
RT plus Cetuximab	5.262	2.839	865899.5896	0.561	0.359	143931	**256,635**	**401,299**
RT alone	4.701	2.480	721968.6878					

**RT- Radiotherapy, LYs- Life years, QALYs- Quality-adjusted life years, ICER- Incremental cost-effectiveness ratio*

Table 11: Undiscounted costs, outcomes and cost- effectiveness of Platinum-based chemotherapy alone and Platinum-based chemotherapy combined with Cetuximab for treatment of recurrent/metastatic squamous cell carcinoma of head and neck cancer in India

Undiscounted Results								
Scenario 1	**Undiscounted LYs**	**Undiscounted QALYs**	**Undiscounted Costs**	**Incremental effects (LYs)**	**Incremental effects (QALYs)**	**Incremental costs**	**ICER (LY)**	**ICER (QALY)**
Platinum-based chemotherapy plus Cetuximab	1.687	0.855	5,31,070	0.034	0.045	146095	**98,55,089**	**75,23,965**
Platinum-based chemotherapy alone	1.653	0.810	1,95,673					
Discounted Results								
Scenario 2	**Discounted LYs**	**Discounted QALYs**	**Discounted Costs**	**Incremental effects (LYs)**	**Incremental effects (QALYs)**	**Incremental costs**	**ICER (LY)**	**ICER (QALY)**

Platinum-based chemotherapy plus Cetuximab	1.646	0.835	5,23,797	0.033	0.043	143931	**1,01,03,902**	**76,47,403**
Platinum-based chemotherapy alone	1.613	0.792	1,91,942					

**RT- Radiotherapy, LYs- Life years, QALYs- Quality-adjusted life years, ICER- Incremental cost-effectiveness ratio*

Discussion

The present study assessed the cost-effectiveness of use of Cetuximab in first line treatment of LA SCCHN and second line treatment of recurrent/metastatic HN cancer patients in India. In the first scenario, we estimated the health and economic outcomes of using RT alone or RT in combination with Cetuximab for the treatment of LA SCCHN patients in India. In the second scenario, we assessed the cost-effectiveness of cetuximab plus platinum-based chemotherapy against platinum-based chemotherapy alone for the treatment of recurrent or metastatic HNSCC in India.

We found that adding cetuximab results in increased costs (ranging between ₹ 5,23,797 to 8,65,899) and health gains (ranging between 0.835-2.83 QALYs) in both scenarios, when treated with platinum-based chemotherapy plus cetuximab and radiotherapy in combination with Cetuximab, respectively. Incremental costs per QALY gained was found to be ₹ 401,299 with use of RT in combination with cetuximab and ₹ 76,47,403 with use of chemotherapy in combination with cetuximab. The ICERs of RT plus cetuximab arm and Platinum-based chemotherapy plus cetuximab arm are 2.3 and 44.5 times the per-capita GDP of India respectively. Hence, Cetuximab is not cost-effective treatment option for patients with LA SCCHN and recurrent/metastatic HNSCC patients respectively in India at the currently recommended willingness to pay (WTP) threshold of per capita GDP. Our study provides compelling evidence on whether to include cetuximab in oncology related health benefit packages under the world's largest health insurance scheme i.e. AB-PMJAY.

The results of the present study are comparable with previous published literature. Two separate economic evaluations found that the use of cetuximab with chemotherapy was not a cost-effective strategy [37, 38].The former study (37) performed in the United Kingdom, found that the incremental cost-effectiveness ratio (ICER) for cetuximab + platinum-based chemotherapy compared with platinum-based chemotherapy of £166,307 (US $218,408/V186,532) per quality adjusted life year (QALY) was considerably above the National Institute for Health and Care Excellence (NICE) threshold of £20,000 to £30,000; therefore, cetuximab in combination with platinum based chemotherapy was not recommended for the treatment of patients with RM-HNSCC. The second study conducted in Canada, reported that cetuximab plus platinum-based chemotherapy compared with platinum-based chemotherapy

alone led to an increase of 0.093 QALY and an increase in cost of CaD $36,000 (US $27,628/V23,590) per patient, resulting in an ICER of CaD $386,000 (US $296,230/V252,935) per QALY gained; thus, the addition of cetuximab to standard platinum-based chemotherapy in first-line treatment of patients with RM-HNSCC reported an ICER that exceeded CaD $100,000 (US $76,732/V65,527) per QALY gained [38]. These findings are in line with the present study results which also showed an incremental gain of 0.033 QALYs with use of cetuximab plus platinum-based chemotherapy compared with platinum-based chemotherapy alone.

We also validated our model with existing published literature. We found that rate of locoregional control in RT alone arm at one-year (59.8%), two-years (41%) and three-years (34%) was in line with the published literature [10]. Similarly, that rate of locoregional control in RT plus cetuximab arm at one-year (71.6%), two-years (52.2%) and three-years (39.9%) was in line with the published literature [10]. Further, the risk of loco-regional recurrence was found to be reduced by 37.2% with use of cetuximab along with RT which is consistent with reported 36% risk reduction in local-regional recurrence with use of cetuximab along with RT [10]. Five-year survival was found to be 52.4% and 63.6% with use of RT alone and RT plus cetuximab respectively, which is again in line with the reported 5-year survival of 17.9% (tongue cancer) to 48.3% (larynx cancer) among LA SSCHN patients in India [26].[Table 12 and Table 13]

Model validation

Table 12: Model validation for Scenario 1 – Radiotherapy alone arm

Effectiveness parameter	Present Study	Published literature	Reference
Loco-regional control rate	One-year LRC rate = 59.8%	One-year LRC rate = 55%	Bonner 2006 trial [10]
	Two-year LRC rate = 39.3%	Two-year LRC rate = 41%	Bonner 2006 trial [10]
	Three-year LRC rate =28.7%	Three-year LRC rate = 34%	Bonner 2006 trial [10]
Risk of locoregional recurrence	One-year LRR rate (RT) = 32.4% One-year LRR rate (RT+C) = 23.6% Which means 37.2% reduction in risk of locoregional progression	36% reduction in risk of locoregional progression	Bonner 2006 trial [10]

Five- year survival	52.4% at 60 months	17.9 % (tongue) to 48.3% (Larynx cancer)	Indian Study by Nandakumar et al 2016 [26]

Table 13: Model validation for Scenario 1 – Radiotherapy combined with Cetuximab

Effectiveness parameter	Present Study	Published literature	Reference
Loco-regional control rate	One-year LRC rate = 71.6%	Two-year LRC rate = 63%	Bonner 2006 trial [10]
	Two-year LRC rate = 52.2%	Two-year LRC rate = 50%	Bonner 2006 trial [10]
	Three-year LRC rate =39.9%	Three-year LRC rate = 47%	Bonner 2006 trial [10]
Risk of locoregional recurrence	One-year LRR rate (RT) = 32.4% One-year LRR rate (RT+C) = 23.6% Which means 37.2% reduction in risk of locoregional progression	36% reduction in risk of locoregional progression	Bonner 2006 trial [10]
Five-year survival	63.6 % at 60 months	17.9 % (tongue) to 48.3% (Larynx cancer) – Indian Study by Nandakumar et al 2016	Indian Study by Nandakumar et al 2016 [26]

Policy Implications

Ayushman Bharat-Pradhan Mantri Jan Aarogya Yojana (AB-PMJAY) [39], which is the flagship health insurance scheme in India, reimburses the use of various chemotherapeutic regimes for HNSCC patients as part of their Health Benefit Package (HBP) 2022 [31]. Our analysis does not support the inclusion of cetuximab at current market price in the package for the treatment of HNSCC. Since there is significant heterogeneity in market prices of chemotherapeutic agents, there is an urgent need to place certain price regulations in place so as to make these drugs more accessible and affordable to HNSCC patients.

Limitations

There are certain limitations of this analysis. Firstly, we have used the international evidence for deriving transition probabilities i.e. movement of patients from PFS to LRR, PFS to DM in scenario I [10] and movement of patients from PFS to DM in scenario II [13]. However, we do not currently have robust country specific data for transition probabilities. Secondly, our model did not account for HPV status. However, although there are solid data on the role of

HPV as prognostic biomarker in head and neck cancer, the benefit of adding cetuximab to chemotherapy in the EXTREME trial was irrespective of the disease HPV status [13]. Thirdly, we have considered the cost of grade 1-2 AEs only for skin rashes and not for other adverse events which might have slightly underestimated the costs. Lastly, we also did not consider the indirect costs due to loss of productivity incurred by the patients as well as the caregivers. This was in agreement with Indian HTA guidelines, [22] and to avoid duplication [40].

Conclusion

The addition of cetuximab to radiotherapy and platinum-based chemotherapy does not provide good value for money in first-line treatment of patients with LA SCCHN and recurrent or metastatic HNSCC respectively. Our study provides an insight and supports the evidence that Cetuximab improves survival and quality of life among LA SCCHN as well as recurrent/metastatic HNSCC cancer patients, but is not cost-effective at current level of WTP threshold in India. Therefore, the present study does not recommend the inclusion of Cetuximab in oncology related health benefit packages under the world's largest health insurance scheme i.e. AB-PMJAY. The study insights can be used for clinical decision-making, guideline development, reimbursement decisions, and price negotiations. Future research may be undertaken to assess the cost-effectiveness of a molecular selection before starting a treatment for Recurrent/metastatic HNSCC including cetuximab as this could limit the use of cetuximab to those who are expected to most likely benefit.

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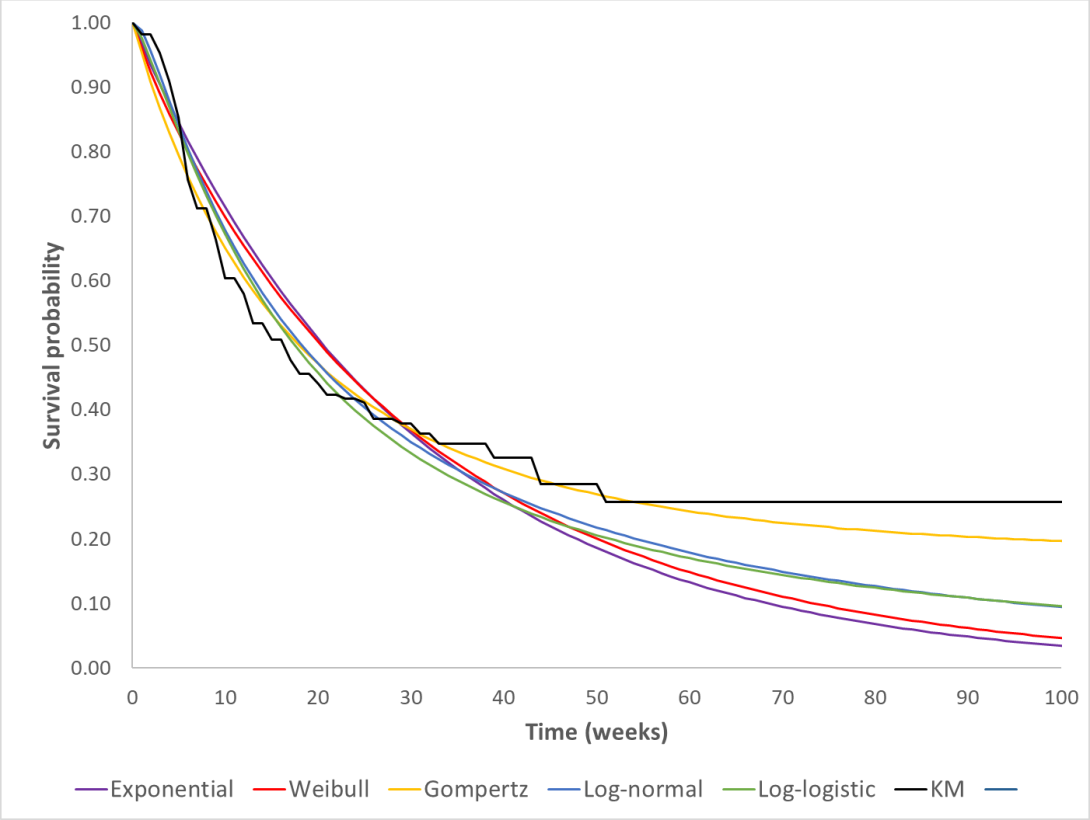

Figure 1: Loco-regional control curve - RT alone

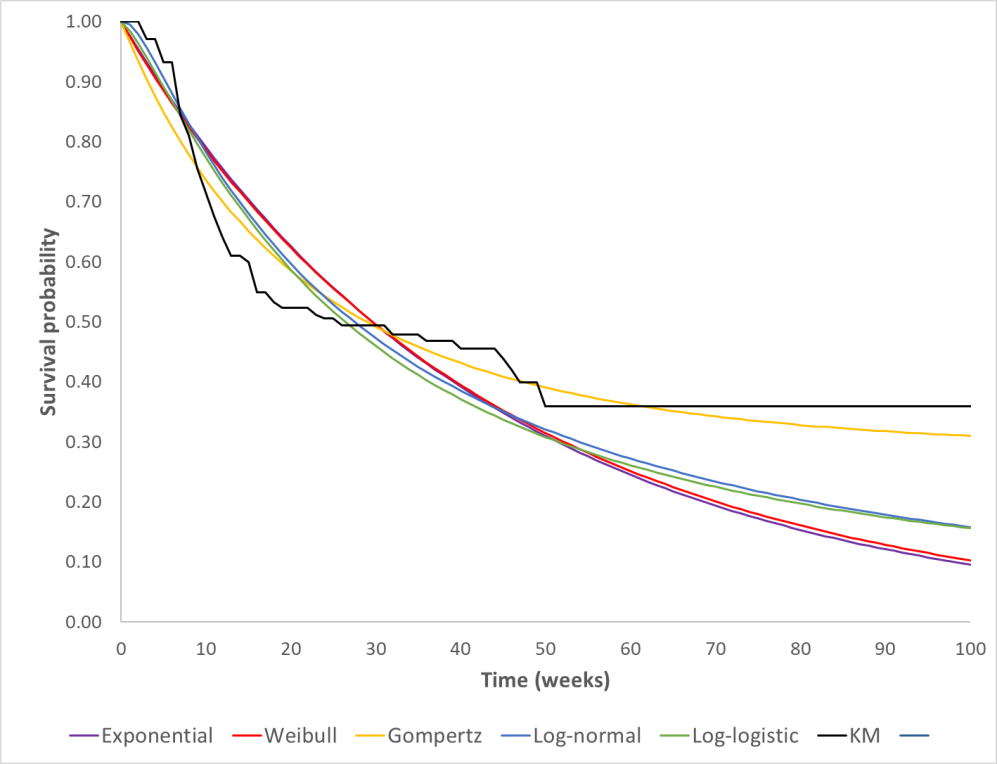

Figure 1 (b) Loco-regional control curve - RT plus Cetuximab

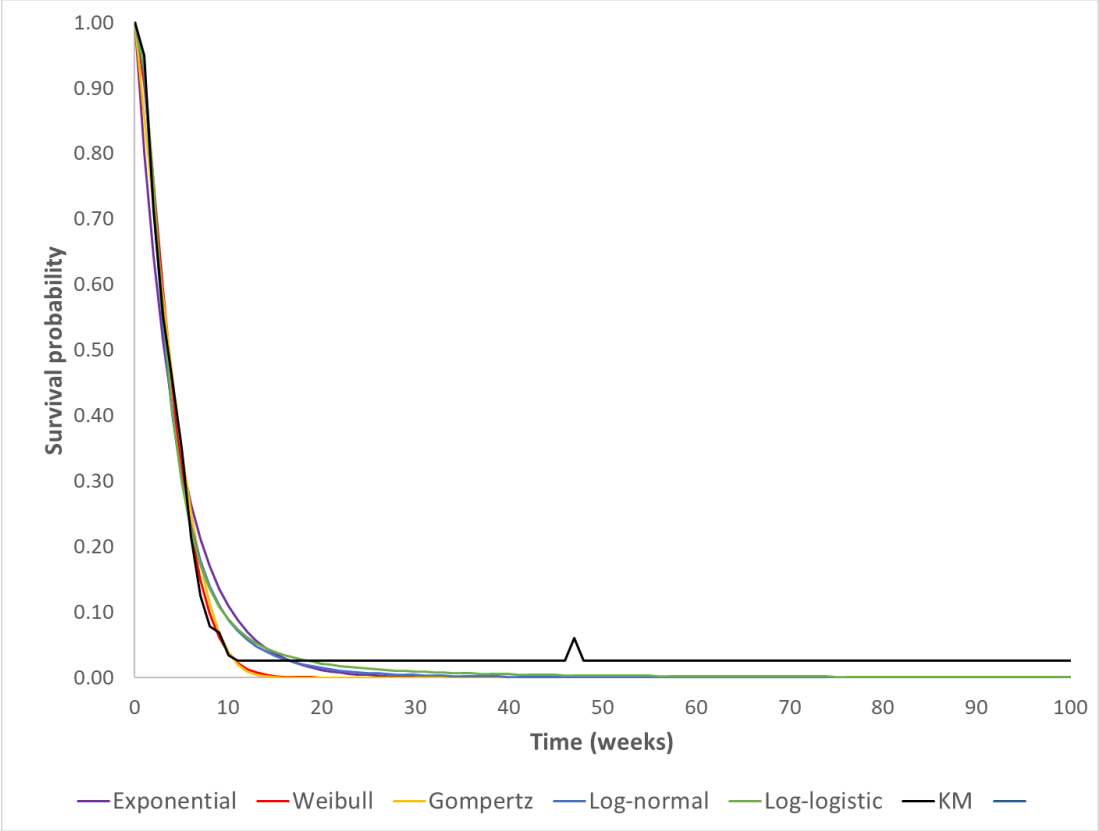

Figure 2 (a) Progression free survival curve – Chemotherapy alone

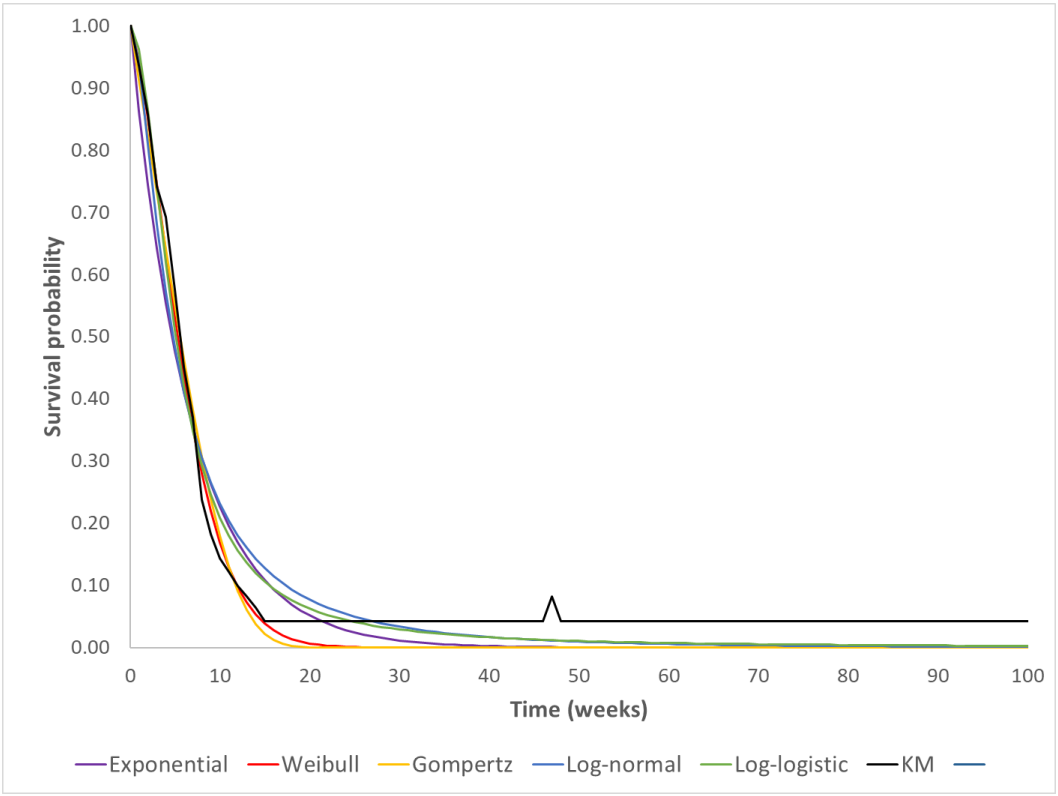

Figure 2 (b) Progression free survival – Chemotherapy plus cetuximab