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► To cite this version:

Lionel Perrier, Frederic Balusson, Magali Morelle, Joël Castelli, Juliette Thariat, et al.. Cost-effectiveness of weekly adaptive radiotherapy versus standard IMRT in head and neck cancer alongside the ARTIX trial. *Radiotherapy & Oncology*, 2024, *Radiotherapy and Oncology: Journal of the European Society For Therapeutic*, 193, pp.110116. 10.1016/j.radonc.2024.110116 . hal-04444231

HAL Id: hal-04444231

<https://hal.science/hal-04444231v1>

Submitted on 23 May 2024

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Original Article



Cost-effectiveness of weekly adaptive radiotherapy versus standard IMRT in head and neck cancer alongside the ARTIX trial

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ARTICLE INFO

Keywords:

Adaptive radiotherapy
Cost-effectiveness
Head and neck cancer
Xerostomia

ABSTRACT

Background and purpose: We performed a cost-effectiveness analysis (CEA) comparing an adaptive radiotherapy (ART) strategy, based on weekly replanning, aiming to correct the parotid gland overdose during treatment and expecting therefore to decrease xerostomia, when compared to a standard IMRT.

Materials and methods: We conducted the ARTIX trial, a randomized, parallel-group, multicentric study comparing a systematic weekly replanning ART to a standard IMRT. The primary endpoint was the frequency of xerostomia at 12 months, measured by stimulating salivary flow with paraffin. The CEA was designed alongside the ARTIX trial which was linked to the French national health data system (SNDS). For each patient, healthcare consumptions and costs were provided by the SNDS. The reference case analysis was based on the primary endpoint of the trial. Sensitivity and scenario analyses were performed.

Results: Of the 129 patients randomly assigned between 2013 and 2018, only 2 records were not linked to the SNDS, which provides a linkage proportion of 98.4%. All of the other 127 records were linked with good to very good robustness. On the intent-to-treat population at 12 months, mean total costs per patient were €41,564 (SD 23,624) and €33,063 (SD 16,886) for ART and standard IMRT arms, respectively ($p = 0.033$). Incremental cost effectiveness ratio (ICER) was €162,444 per xerostomia avoided. At 24 months, ICER was €194,521 per xerostomia avoided. For both progression-free and overall survival, ART was dominated by standard IMRT.

Conclusion: The ART strategy was deemed to be not cost-effective compared with standard IMRT for patients with locally advanced oropharyngeal cancer.

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Background

Radiation therapy is a standard treatment for patients with locally advanced squamous cell carcinoma of the head and neck [1,2]. Among the existing radiotherapy techniques, intensity modulated radiotherapy (IMRT) is the recommended treatment [3]. Indeed, this technique makes it possible to reduce the doses of radiation administered to the parotid glands at the planning stage and thus to reduce xerostomia in these patients [4–6]. The parotid glands are the major tissues responsible for salivary output, contributing up to 70% of the salivary flow [7]. Radiation-related xerostomia consists of a dry mouth resulting from radiation-induced damage to the salivary gland.

IMRT classically includes an initial pre-treatment planning, while large anatomical variations are observed during the treatments, such as shrinkage of the tumor and the parotid gland. These variations may result in parotid gland overdose and thus increase the risk of xerostomia. Adaptive radiotherapy (ART), which includes several replanning sessions, aims to correct parotid gland overdose during the treatment course, thus potentially reducing xerostomia [8–11]. The literature reports a benefit of ART in reducing the dose in the parotid glands [9,11–14].

We conducted the ARTIX trial, a randomized, parallel-group, multicenter study comparing systematic weekly replanning ART with single planning based IMRT in locally advanced oropharynx carcinomas. We tested a systematic maximalist weekly replanning ART approach. We showed that ART appears to be technically feasible and safe and does not decrease local disease control and survival [15]. The rate of xerostomia grade ≥ 2 at 12 months was 51.8% [95% CI: 37.5%-62.9%] in the ART arm, compared to 53.5% [95% CI: 39.4%-64.3%] in the standard arm ($P = 0.98$) [15].

To our knowledge, none of the published studies dealing with ART has explored the medico-economic impact of this treatment. Therefore, in this study we conducted a cost-effectiveness analysis (CEA) alongside the ARTIX phase-III trial matched to the French national health insurance database (SNDS).

Methods

Study design

The ARTIX trial, a randomized, parallel-group, multicenter study comparing systematic weekly replanning (ART) with standard IMRT (without replanning), was conducted in 11 French centers. In brief, patients were randomized 1:1 to receive standard IMRT or ART, combined in all cases to systemic treatment. All of the patients received a total dose of 70 Gy in 35 fractions (2 Gy/fraction/day). For the patients in the ART arm, a weekly computed tomography scan was performed using the same protocol as the initial planning CT, except for some variations in intravenous contrast agent use. The dose distribution was computed using the same constraints as those used in the initial planning. A maximum of 4 days was allowed between each weekly CT scan and the start of the treatment using a new dose distribution. One planning, based on the radiation oncologist's decision, was allowed in the standard IMRT arm. Full details have been published elsewhere [15].

Primary endpoint of the randomized study

The primary endpoint was the frequency of xerostomia defined by salivary quantification 12 months after the end of radiotherapy. The salivary flow was measured for primary analysis using stimulation by chewing paraffin wax before radiotherapy (baseline) and at 6, 12, 18, and 24 months after radiotherapy. The patient chewed paraffin wax for 2 min, and while continuing chewing, saliva was collected for 5 min. The salivary flow was measured using the formula: weight of the saliva sample/sample collection time in minutes (mg/min). A salivary flow of ≤ 500 mg/min was used as the threshold for xerostomia [15,16].

Cost data

Costs, in EUR 2020, were broken down by the French national health insurance system. The time horizon covered the period of 12 and 24 months after the end of radiotherapy. Individual healthcare consumptions and costs for patients included in the trial were provided by the French national health data system (SNDS) [17]. More precisely, the project was to link the ARTIX trial to a dataset extracted from the SNDS comprising 22,426 adults selected on the basis of having cancer cared for in one of the 11 participating clinical centers. We preprocessed the two datasets to harmonize the variable names and values. After data preprocessing, we proceeded with duplicate checks. Full details of the linkage have been published elsewhere [18]. Costs at 24 months were discounted at a 2.5% rate considering the guidelines of the French National Authority for Health [19]. This economic ARTOME study (NCT05025618) was approved by the French National Committee on Informatics and Privacy (Commission Nationale de l'Informatique et des Libertés, N°916915).

Effectiveness and cost-effectiveness analysis

The main analysis was based on the primary endpoint of the ARTIX trial and on the intent-to-treat population (ITT). Scenario analyses were performed based on the salivary flow as well as the progression-free survival (PFS) and overall survival (OS) at 24 months. Incremental cost-effectiveness ratios (ICER) comparing ART versus standard IMRT were calculated as follows:

$$ICER = \frac{Averagecost_{ART} - Averagecost_{StandardIMRT}}{Averageeffectiveness_{ART} - Averageeffectiveness_{StandardIMRT}}$$

where costs were measured in EUR 2020 and effects in salivary flow, PFS, and OS.

Incremental costs and incremental effects were represented using the incremental cost-effectiveness plane [20]. The horizontal and the vertical axes divide the plane according to incremental cost and incremental effect, respectively. Thus, the incremental cost-effectiveness plane comprises four quadrants through the origin: if the ICER for ART versus standard IMRT were positioned in the southeast quadrant, this would mean that ART is less costly and more effective than standard IMRT (i.e., ART dominates standard IMRT). Conversely, if the ICER were positioned in the northwest quadrant, this would mean that ART is more expensive and less effective than standard IMRT (i.e., ART is dominated by standard IMRT). In the two other quadrants, ART may be considered cost-effective depending upon the value at which the ICER is considered good value for money based on a specified monetary threshold (the threshold represents the maximum acceptable ceiling ratio) [21].

Statistical analysis

The analyses were conducted in both ITT and per protocol (PP) populations. Descriptive statistics were used in order to present patients' characteristics, treatment costs, and health outcomes. Costs were compared using the Wilcoxon-Mann-Whitney test. One-way sensitivity analyses were conducted by varying cost and effect parameters by plus or minus 20% and illustrated graphically in a tornado diagram. Uncertainty was handled using non-parametric bootstrap methods as recommended [19]. The cost-effectiveness acceptability curves (CEAC) were generated by plotting the probability (y-axis) that the ART strategy would be cost-effective over a range of willingness-to-pay thresholds (x-axis) [22]. All statistical analyses were performed using the World Programming System (WPS) software and Treeplan SensIt®. A p-value of less than 0.05 was considered to indicate statistical significance. The study results were reported according to standard guidelines for economic evaluation [23].

Results

A total of 132 patients were included in the ARTIX trial, running from July 2013 to October 2018. Since 3 patients did not consent and 2 patients did not match with the SNDS, 127 patients were enrolled in the ITT cost-effectiveness analysis. The flow chart of the patient population is presented in Fig. 1. Baseline patients' characteristics were similar between the arms. Details have been provided elsewhere and in Appendix 1.

Only 2 records among the 129 records were not linked due to a lack of information in the trial, providing a linkage proportion of 98.4%. All of the other 127 records were linked with good ($R = 2$) to very good ($R = 7$) robustness. A minimum robustness of 2 indicates that the linked pairs are very reliable. The linkage robustness was 4.18. Details are provided in Appendix 2.

Table 1 reports healthcare consumption. The mean total costs per patient at 12 months were €41,564 (SD 23,624) and €33,063 (SD 16,886) for ART and standard IMRT arms, respectively ($p = 0.033$). At 24 months, costs were €51,150 (SD 30,962) and €41,308 (SD 23,561), respectively ($p = 0.092$). The largest portion of the total cost was represented by the costs of hospitalization. All costs details are reported in Table 2.

At 12 months, 19 out of 64 patients had xerostomia in the ART arm and 22 out of 63 in the standard IMRT arm. The ICER, corresponding to the mean difference in costs (€8,501) divided by the mean difference in effect (0.0523), was €162,444 per xerostomia avoided¹.

The incremental cost-effectiveness plane is represented in Appendix 3. Fig. 2 shows that the most sensitive parameter was the difference in effect. A 50% reduction of the number of patients with xerostomia in the ART arm would have reduced ICER from €162,444 to €42,342 per xerostomia avoided. Further calculations are provided in Appendix 4. The scatter plot of bootstrapped ICER in the cost-effectiveness plane is presented in Fig. 3a. The probability was the highest for the northeast quadrant (73.8%), in which the ART arm was both costlier and more effective than in the IMRT arm. Results were robust at 50%. The acceptability curve is presented in Fig. 4a. The probability of ART strategy being cost-effective did not exceeded 70% at high level of willingness to pay.

At 24 months, 12 out of 64 patients in the ART arm had xerostomia compared to 15 out of 63 in the standard IMRT arm. Difference in costs was €9,842, and difference in effect 0.0506. The ICER was €194,529 per xerostomia avoided². The scatter plot of bootstrapped ICER is presented in Fig. 3b. The probability was the highest for the northeast quadrant (75.6%), in which the ART arm was both costlier and more effective than in the IMRT arm. The probability of ART strategy being cost-effective did not exceeded 70% at high level of willingness to pay (cf. Fig. 4b). For PFS, the difference in costs was €9,842, and the difference in effect -0.008 . ART was dominated by standard IMRT. The probabilities were the highest for the northwest quadrant (cf. Fig. 3c). The probability of ART strategy being cost-effective did not exceeded 50% at a high level of willingness to pay (cf. Fig. 4c). For OS, the difference in costs was €9,842, and the difference in effect -0.037 . ART was dominated by standard IMRT. The probabilities were the highest for the northwest quadrant (cf. Fig. 3d). The probability of ART strategy being cost-effective did not exceeded 30% at high level of willingness to pay (cf. Fig. 4d).

In the PP population, the ICER were €271,252 and €568,869 per xerostomia avoided at 12 and 24 months respectively. For PFS, the ICER was €168,919 per PF-LFG. For OS, ART was dominated by standard

IMRT. Details are provided in Appendix 5.

Discussion

To the best of our knowledge, this is the first study to evaluate the cost-effectiveness of replanning ART. The expenses that explain the higher cost of the ART strategy are mainly due to the cost of replanning (€2,923 vs. €66 per patient, $p < 0.001$). In the ITT population, ICERs were €162,444 and €194,529 per xerostomia avoided at 12 and 24 months, respectively. The ICER are too high to consider that ART is a cost-effective technique. Pichon-Riviere et al. estimate cost-effectiveness thresholds based on per-capita health expenditures and life expectancy for France at US\$40,006 (at their value in 2019) per quality-adjusted life year (QALY) and US\$34,815 (again, at their 2019 value) per life year [24]. In our study, replanning ART was dominated by standard IMRT when progression-free and overall survival were taken into account.

In their recent review of the literature, Avgousti et al. identify a total of 85 studies on the topic of ART using the PRISMA methodology [25]. Most of the studies ($N = 70$) were general reviews and 13 studies included a small number of patients. Only a few studies revealed a clear benefit of ART. Avgousti et al. conclude that even though changes in the anatomy of patients occurred, several replanning sessions were not always necessary, as far as the initial plan was still acceptable; our results seem to be consistent with these findings. The absence of benefits of ART in this study can be explained with a number of different reasons: (i) The submandibular glands and oral cavity glands were not specifically spared in the study, although they, in addition to the parotid glands, also contribute to salivary flow. It is likely that a only specific subgroup of patients and not the whole tested population benefits from the ART strategy because only a subgroup of the patients had a parotid gland overdose. The clinical benefit of ART is underestimated in this population. (ii) While the randomized study failed to demonstrate the clinical benefits of ART, the ART strategy was, however, found to significantly improve the parotid gland salivary flow assessed by salivary scintigraphy. More precise identification of good candidate patients is likely to lower ICERs and make the ART strategy acceptable in this sub-population.

Our study provides useful information regarding replanning sessions in locally advanced oropharynx carcinoma. The present study adds to the still limited body of cost-effectiveness of IMRT in this indication [26–32]. It is all the more important as, to our knowledge, IMRT seems to be the most cost-effective radiotherapy technique in this indication in high income countries³ compared to three-dimensional conformal radiation therapy (3DCRT) and intensity modulated proton beam therapy (PBT). Hence, any evolution of this technique must be analyzed with attention, including from a health-economic point of view. In fact, Yong et al. [32] report an increase in cost per QALY of \$5,084 for IMRT compared to 3DCRT. Sher et al. compared the cost-effectiveness of IMRT with PBT in the management of stage III-IVB oropharynx cancer [30]. Nearly every scenario reports ICERs above \$150,000/QALY, and even \$288,000 and \$390,000 per QALY gained for favorable human papillomavirus-positive oropharynx cancer in the payer and societal perspective, respectively. Thus, studies that evaluate technical, organizational, and clinical practice innovations to improve IMRT, such as ART which is in its infancy, should be encouraged.

The present CEA was conducted alongside the ARTIX Randomized Clinical Trial matched to the SNDS. This methodology allowed us to access exhaustive data on all health-spending reimbursements for each

¹ At12monthsICER = $\frac{€41,564 - €33,063}{0.0523} = \frac{€8,501}{0.0523} = €162,444$ per xerostomia avoided.

² At24monthsICER = $\frac{€51,150 - €41,308}{0.0506} = \frac{€9,842}{0.0506} = €194,529$ per xerostomia avoided.

³ One to three gross domestic product (GDP) per capita are the most commonly used cost-effectiveness decision-making thresholds in CEA studies in low- and middle-income countries [33]. For example, Chauhan et al. conclude that both IMRT and 3D-CRT are not cost-effective when compared with 2D radiotherapy at 1 time GDP per capita for treating head and neck cancers in India [26].

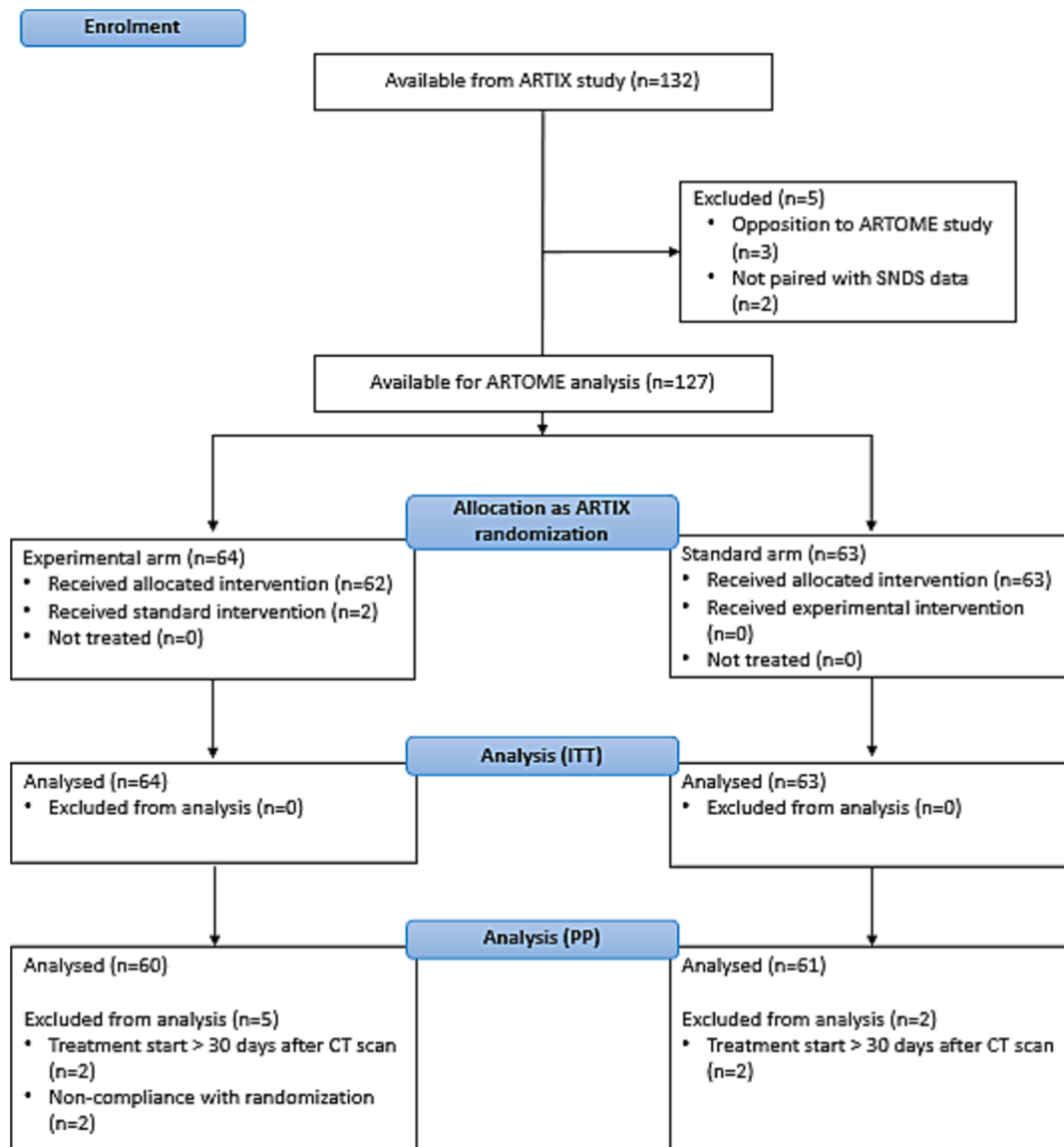


Fig. 1. Flowchart of the patient population.

patient included in the study [17,34]. Daval reports that common collection tools, such as case report forms, underestimate the consumption of healthcare resources and its associated costs, particularly for ambulatory care [35]. They show that hospital admissions are underestimated by 13% (95% CI: 8–20), corresponding costs by 5% (95% CI: 2–14), and ambulatory acts by 41% (95% CI: 33–51), with large variations in costs depending on the study. Matching the ARTIX Randomized Clinical Trial and the SNDS is a strength of this study. To the best of our knowledge, this is the first CEA based on a Randomized Clinical Trial matched to the SNDS. Challenges could arise in linking routinely collected data to other sources of data, including linkage errors when records cannot be linked or are linked incorrectly. This was not the case in our study, since the linkage proportion was 98.4% [18].

Finally, performing a CEA of the ARTIX trial was appropriate even if the difference in effect was not statistically significant in this clinical study. Indeed, the interest of the health economics evaluation is not in clinical difference alone, but in the joint distribution of cost and effect differences that may indicate a weight of evidence favoring one treatment over another. The analytic focus should be on the estimation of the joint density of cost and effect differences, and the quantification of uncertainty surrounding the ICER [36].

Moreover, publishing economic evaluations for both positive and negative trials reduces the publication bias in systematic reviews [37]. It is also recommended that CEA is performed instead of a cost-minimization analysis, even if the differences in effect are not significant [38]. Even if the clinical benefit of ART was not demonstrated in this trial, our CEA could also provide data that could be used in establishing assumptions in future health economics analysis in ART.

This study had some limitations. First, the perspective of the French national health insurance was retained, meaning that both the out-of-pocket spending by informal carers and productivity loss were not assessed. The costs directly supported by the hospital (e.g., time “lost” for rescheduling the use of processing machines) are included indirectly through the use of tariffs. Other methods (e.g., micro-costing, activity-based costing) used for several radiotherapy techniques, e.g., 3DCRT, IMRT, image-guided radiotherapy (IGRT), and stereotactic body radiation therapy (SBRT), can be used to better specify these costs [39–41].

Secondly, differences in national and/or insurance reimbursement systems (e.g., hospital budgets, payment per episode-of-care, payment per treatment fraction/fee-for-service) may limit the generalizability of our results [42,43]. In the United States, the expected radiation oncology alternative payment model (RO-APM) reimbursement for

Table 1
Mean healthcare consumption per patient in the ART and standard IMRT arms.

	Time horizon 12 months			Time horizon 24 months		
	ART arm (n = 64) Mean (SD)	IMRT arm (n = 63) Mean (SD)	p-value ^a	ART arm (n = 64) Mean (SD)	IMRT arm (n = 63) Mean (SD)	p-value ^a
HOSPITALIZATIONS						
Number of acute care hospital stays	29.59 (12.83)	29.84 (11.54)	0.890	32.20 (16.62)	33.78 (15.74)	0.523
Number of home care hospitalizations	0.22 (1.75)	0.08 (0.63)	1.000	0.27 (1.78)	0.08 (0.63)	0.570
Number of follow-up and rehabilitation care hospital stays	0.25 (0.75)	0.25 (0.76)	0.803	0.48 (1.13)	0.27 (0.79)	0.310
OUTPATIENT TREATMENT						
Number of nurse visits	180.61 (215.38)	127.17 (152.12)	0.105	216.19 (275.27)	157.17 (179.23)	0.164
Number of physiotherapy visits	12.03 (19.92)	7.62 (13.62)	0.404	19.25 (29.01)	12.95 (25.90)	0.110
Number of GP and specialist visits	14.73 (8.59)	13.40 (7.29)	0.409	23.66 (14.33)	21.56 (11.65)	0.581
REPLANNING^b						
	Frequency (%)	Frequency (%)				
0	2 (3.13)	56 (88.89)				
1	1 (1.56)	7 (11.11)				
2	0 (3.13)	0				
3	0 (0)	0				
4	0 (0)	0				
5	50 (78.13)	0				
6	11 (17.19)	0				

^a Wilcoxon-Mann-Whitney test.

^b The frequencies of replannings at 12 and 24 months are the same.

Table 2
Mean total costs per patient in the ART and standard IMRT arms.

Costs (in € 2020)	Time horizon 12 months			Time horizon 24 months		
	ART arm (n = 64) Mean (SD)	IMRT arm (n = 63) Mean (SD)	p-value ^a	ART arm (n = 64) Mean (SD)	IMRT arm (n = 63) Mean (SD)	p-value ^a
HOSPITALIZATIONS						
Acute care hospitalization	30,275 (23,346)	25,467 (16,639)	0.372	37,304 (29,456)	31,206 (20,701)	0.500
<i>Incl. Diagnosis-related groups</i>	<i>16,809 (9,634)</i>	<i>15,884 (8,992)</i>	<i>0.446</i>	<i>19,579 (12,534)</i>	<i>19,238 (11,758)</i>	<i>0.776</i>
<i>Resuscitation unit</i>	<i>2,360 (9,987)</i>	<i>205 (1,324)</i>	<i>0.436</i>	<i>2,360 (9,987)</i>	<i>205 (1,324)</i>	<i>0.436</i>
<i>Intensive care</i>	<i>248 (1,454)</i>	<i>13 (101)</i>	<i>0.315</i>	<i>328 (1,511)</i>	<i>88 (310)</i>	<i>0.959</i>
<i>Expensive medical devices</i>	<i>13 (106)</i>	<i>135 (684)</i>	<i>0.300</i>	<i>38 (173)</i>	<i>135 (684)</i>	<i>0.969</i>
<i>Expensive drugs</i>	<i>2,392 (4,514)</i>	<i>1,262 (2,604)</i>	<i>0.188</i>	<i>3,590 (7,143)</i>	<i>3,457 (6,775)</i>	<i>0.640</i>
Home care hospitalization	825 (6,538)	554 (4,352)	1.000	972 (6,623)	554 (4,352)	0.570
Follow-up and rehabilitation care	1,858 (6,203)	1,546 (4,787)	0.826	4,266 (11,152)	1,239 (4,402)	0.283
Transportation	3,191 (1,370)	3,218 (1,232)	0.890	3,465 (1,762)	3,632 (1,665)	0.496
REPLANNING	2,923 (646)	66 (185)	< 0.001	2,923 (646)	66 (185)	< 0.001
OUTPATIENT TREATMENT						
<i>Nurse visits</i>	<i>7,871 (5,490)</i>	<i>6,704 (3,800)</i>	<i>0.354</i>	<i>10,165 (7,014)</i>	<i>9,080 (6,233)</i>	<i>0.388</i>
<i>Physiotherapy visits</i>	<i>1,900 (2,667)</i>	<i>1,022 (1,181)</i>	<i>0.052</i>	<i>2,257 (3,317)</i>	<i>1,259 (1,374)</i>	<i>0.130</i>
<i>Pharmacy</i>	<i>210 (345)</i>	<i>139 (253)</i>	<i>0.393</i>	<i>337 (503)</i>	<i>234 (475)</i>	<i>0.109</i>
<i>Biology</i>	<i>1,271 (1,240)</i>	<i>1,462 (1,348)</i>	<i>0.569</i>	<i>1,733 (1,470)</i>	<i>2,064 (1,858)</i>	<i>0.732</i>
<i>Transport (cab/VSL)</i>	<i>296 (295)</i>	<i>290 (234)</i>	<i>0.645</i>	<i>456 (396)</i>	<i>468 (376)</i>	<i>0.700</i>
<i>GP and specialist visits</i>	<i>3,558 (3,160)</i>	<i>3,210 (2,849)</i>	<i>0.626</i>	<i>4,234 (4,041)</i>	<i>4,003 (4,239)</i>	<i>0.736</i>
<i>Imaging</i>	<i>379 (256)</i>	<i>325 (178)</i>	<i>0.371</i>	<i>598 (379)</i>	<i>518 (280)</i>	<i>0.414</i>
<i>Imaging</i>	<i>255 (218)</i>	<i>256 (222)</i>	<i>0.983</i>	<i>550 (353)</i>	<i>534 (345)</i>	<i>0.815</i>
OUTPATIENT AND VISITS (private institutions)	495 (1,457)	826 (2,342)	0.677	758 (2,374)	956 (2,588)	0.726
TOTAL COST	41,564 (23,624)	33,063 (16,886)	0.033	51,150 (30,962)	41,308 (23,561)	0.092

^a Wilcoxon-Mann-Whitney test.

centers for Medicare and Medicaid Services is \$20,504 for head and neck cancer (2D 4 fractions QUADSHOT, 2D 28 fractions larynx, or IMRT 30 fractions definitive) [44].

Third, the trial ARTIX, which began in 2012, did not allow for the assessment of outcome in cost per QALY. Despite these limitations, this study, which was designed prospectively and within the context of a randomized clinical trial, contributes to our understanding of the appropriate cost and effectiveness of replanning ART compared with standard IMRT.

Conclusion

This study provides useful and practical information about replanning ART with standard IMRT for decision makers, including hospital managers.

Funding

The French National Cancer Institute and the French Ministry of Social Affairs code project (PAIR VADS 2011 grant, PRME-K

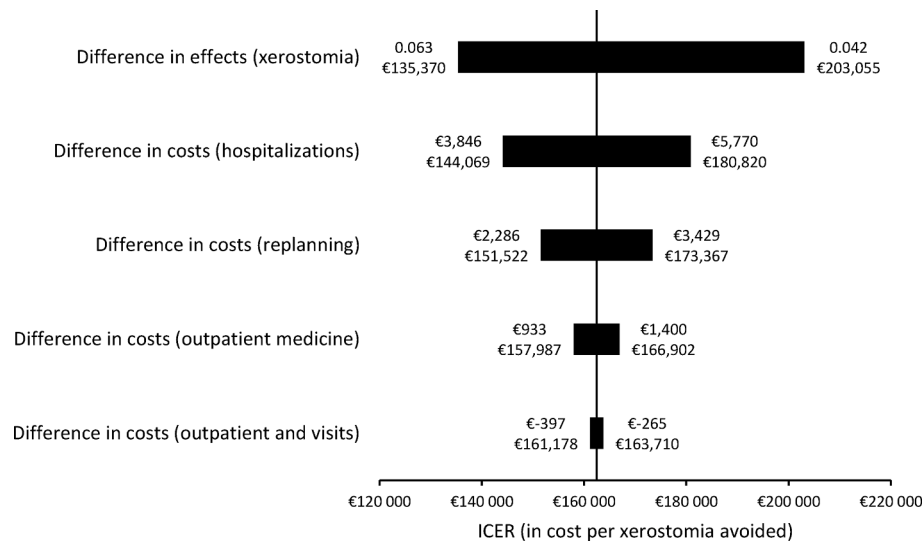


Fig. 2. One-way sensitivity analysis of the ICER per xerostomia avoided at 12 months. The tornado diagram illustrates the impact of a variation of $\pm 20\%$ on the value of each parameter. The length of each bar represents the extent to which the ICER is sensitive to this parameter. The graph is laid out so that the most sensitive parameter (the one with the longest bar) is at the top, and the least sensitive is at the bottom. The vertical line represents the ICER when all parameters assume their base values (€162,444 per xerostomia avoided). Increasing the mean difference in effect by 20% (i.e., from 0.0523 to 0.063) decreases the ICER from €162,444 to €135,370.

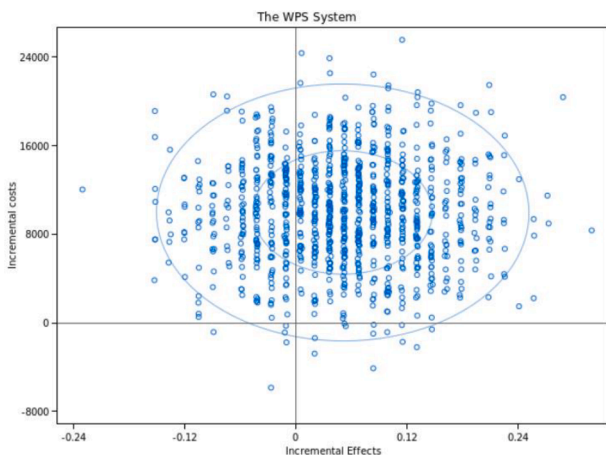


Fig. 3a. Scatter plots of the joint density of incremental costs and incremental effects of ART vs. standard IMRT by bootstrap re-sampling. The scatter plots illustrate the uncertainty surrounding the estimates of expected incremental costs (in EUR 2020) and expected incremental effects (in xerostomia avoided, progression-free life year, and life year) associated with ART compared to standard IMRT. For example, in Fig. 3a the location and the spread of the points in the horizontal plane indicate that there is uncertainty regarding the existence of a benefit in terms of xerostomia associated with ART compared to standard IMRT. This is consistent with the fact that the ARTIX failed to meet its primary endpoint with no statistically significant difference in rates of clinically relevant xerostomia at 12 months following treatment. Fig. 3a. Xerostomia avoided at 12 months.

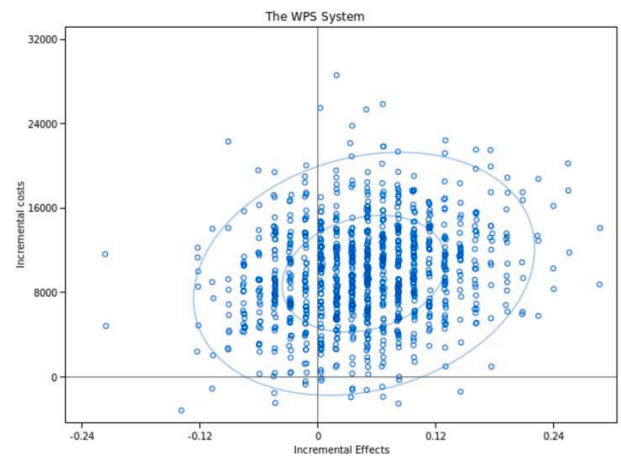


Fig. 3b. Xerostomia avoided at 24 months.

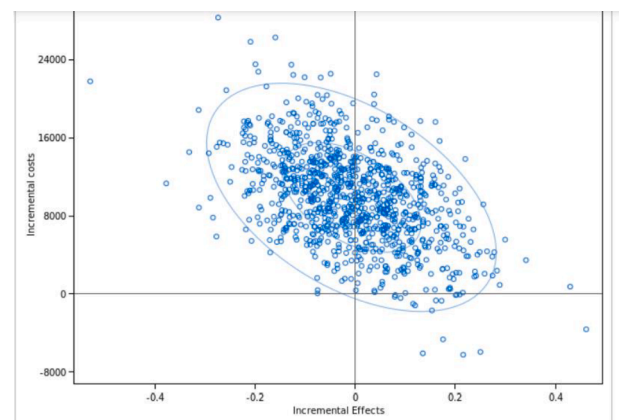


Fig. 3c. Progression-free life year at 24 months.

1469021N). The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The authors declare that they have no known competing financial interests.

CRediT authorship contribution statement

Lionel Perrier: Conceptualization, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Frédéric Balusson:** Formal

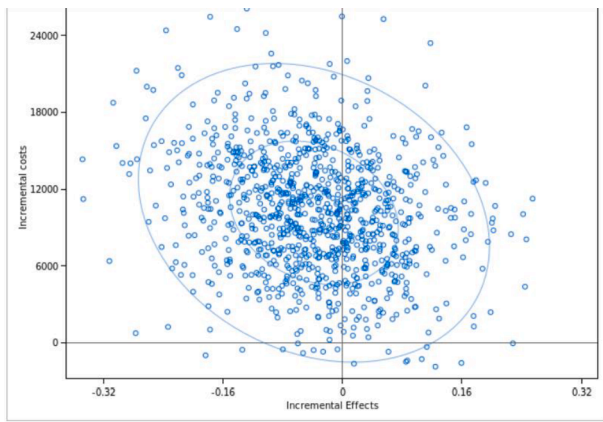


Fig. 3d. Life year at 24 months.

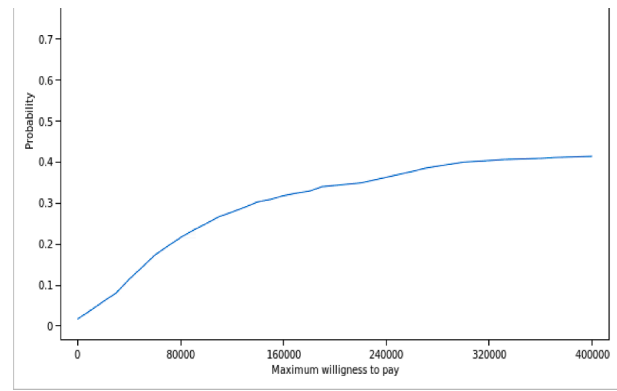


Fig. 4c. Per progression-free life year at 24 months.

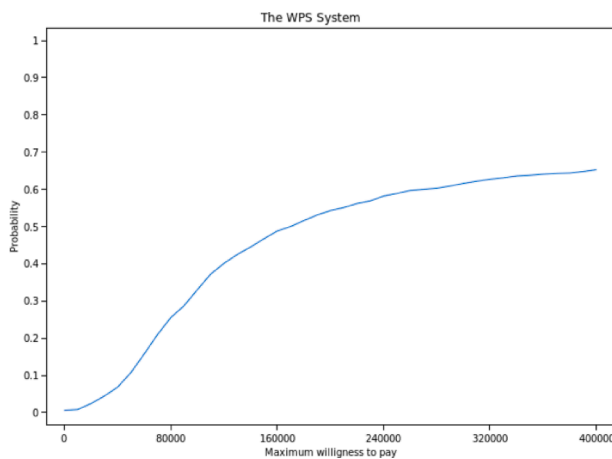


Fig. 4a. Cost-effectiveness acceptability curves showing the probability that ART is cost-effective compared to standard IMRT (y-axis) over a range of willingness-to-pay thresholds (x-axis). The CEACs show the probability that ART is cost-effective compared with standard IMRT (y-axis) for a range of values that the decision-maker might consider to be the maximum cost they are willing to pay for a gain of one unit of effect (x-axis). For example, in Fig. 4a ART has a probability of 0.5 to be cost-effective compared with standard IMRT if the decision-maker were to consider €160,000 to be the maximum cost they are willing to pay for a gain of one xerostomia avoided at 12 months. Fig. 4a. Per xerostomia avoided at 12 months.

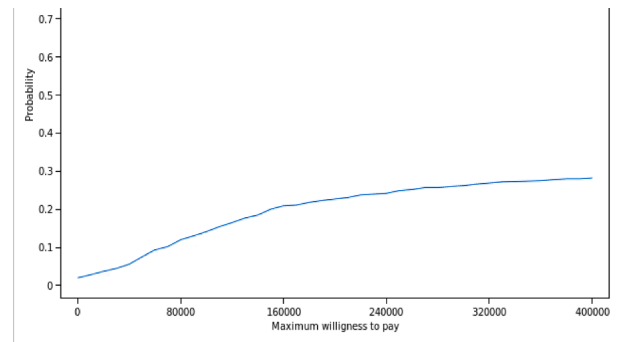


Fig. 4d. Per life year at 24 months.

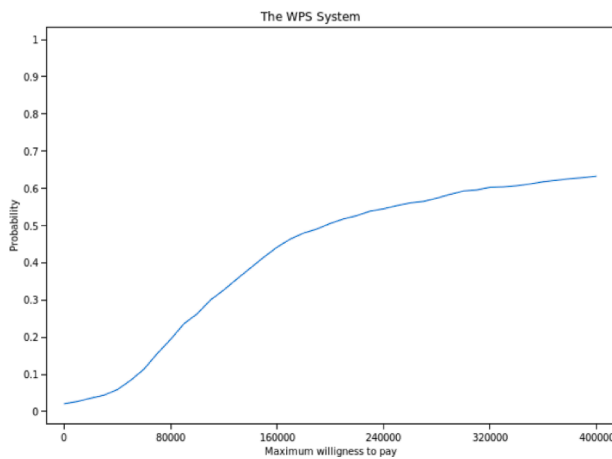


Fig. 4b. Per xerostomia avoided at 24 months.

analysis, Investigation, Methodology, Software, Validation. **Magali Morelle:** Formal analysis, Investigation, Methodology, Software. **Joël Castelli:** Formal analysis, Investigation, Methodology, Validation. **Juliette Thariat:** Investigation. **Karen Benezery:** Investigation. **Ali Hasbini:** Investigation. **Bernard Gery:** Investigation. **Antoine Berger:** Investigation. **Xavier Liem:** Investigation. **Sébastien Guihard:** Investigation. **Sophie Chapet:** Investigation. **Sébastien Thureau:** Investigation. **Pierre Auberdiac:** Investigation. **Pascal Pommier:** Investigation. **Amandine Ruffier:** Investigation. **Anne Devillers:** Investigation. **Emmanuel Oger:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Supervision, Validation. **Boris Campillo-Gimenez:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation. **Renaud de Crevoisier:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2024.110116>.

References

[1] Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–78. <https://doi.org/10.1056/NEJMoa053422>.

- [2] Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;11:21–8. [https://doi.org/10.1016/S1470-2045\(09\)70311-0](https://doi.org/10.1016/S1470-2045(09)70311-0).
- [3] Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet Lond Engl* 2019;393:40–50. [https://doi.org/10.1016/S0140-6736\(18\)32779-X](https://doi.org/10.1016/S0140-6736(18)32779-X).
- [4] Kam MKM, Leung S-F, Zee B, Chau RMC, Suen JJS, Mo F, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol* 2007;25:4873–9. <https://doi.org/10.1200/JCO.2007.11.5501>.
- [5] Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;12:127–36. [https://doi.org/10.1016/S1470-2045\(10\)70290-4](https://doi.org/10.1016/S1470-2045(10)70290-4).
- [6] Pow EHN, Kwong DLW, McMillan AS, Wong MCM, Sham JST, Leung LHT, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006;66:981–91. <https://doi.org/10.1016/j.ijrobp.2006.06.013>.
- [7] Murthy V, Lewis S, Kannan S, Khadanga CR, Rangarajan V, Joshi K, et al. Submandibular function recovery after IMRT in head and neck cancer: a prospective dose modelling study. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2018;129:38–43. <https://doi.org/10.1016/j.radonc.2018.02.021>.
- [8] Castelli J, Simon A, Lafond C, Perichon N, Rigaud B, Chajon E, et al. Adaptive radiotherapy for head and neck cancer. *Acta Oncol Stockh Swed* 2018;57:1284–92. <https://doi.org/10.1080/0284186X.2018.1505053>.
- [9] Castelli J, Simon A, Louvel G, Henry O, Chajon E, Nassef M, et al. Impact of head and neck cancer adaptive radiotherapy to spare the parotid glands and decrease the risk of xerostomia. *Radiat Oncol Lond Engl* 2015;10:6. <https://doi.org/10.1186/s13014-014-0318-z>.
- [10] Ahn PH, Chen C-C, Ahn AI, Hong L, Sripes PG, Shen J, et al. Adaptive planning in intensity-modulated radiation therapy for head and neck cancers: single-institution experience and clinical implications. *Int J Radiat Oncol Biol Phys* 2011;80:677–85. <https://doi.org/10.1016/j.ijrobp.2010.03.014>.
- [11] Jensen AD, Nill S, Huber PE, Bendl R, Debus J, Mütter MW. A clinical concept for interfractional adaptive radiation therapy in the treatment of head and neck cancer. *Int J Radiat Oncol Biol Phys* 2012;82:590–6. <https://doi.org/10.1016/j.ijrobp.2010.10.072>.
- [12] Zhao L, Wan Q, Zhou Y, Deng X, Xie C, Wu S. The role of replanning in fractionated intensity modulated radiotherapy for nasopharyngeal carcinoma. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2011;98:23–7. <https://doi.org/10.1016/j.radonc.2010.10.009>.
- [13] Kataria T, Gupta D, Goyal S, Bisht SS, Basu T, Abhishek A, et al. Clinical outcomes of adaptive radiotherapy in head and neck cancers. *Br J Radiol* 2016;89:20160085. <https://doi.org/10.1259/bjr.20160085>.
- [14] Schwartz DL, Garden AS, Thomas J, Chen Y, Zhang Y, Lewin J, et al. Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial. *Int J Radiat Oncol Biol Phys* 2012;83:986–93. <https://doi.org/10.1016/j.ijrobp.2011.08.017>.
- [15] Castelli J, Thariat J, Benezery K, Hasbini A, Gery B, Berger A, et al. Weekly adaptive radiotherapy vs standard intensity-modulated radiotherapy for improving salivary function in patients with head and neck cancer: a phase 3 randomized clinical trial. *JAMA Oncol* 2023. <https://doi.org/10.1001/jamaoncol.2023.1352>.
- [16] Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. *Oral Dis* 2002;8:117–29. <https://doi.org/10.1034/j.1601-0825.2002.02851.x>.
- [17] Rachas A, Gastaldi-Ménager C, Denis P, Barthélémy P, Constantinou P, Drouin J, et al. The economic burden of disease in France from the national health insurance perspective: the healthcare expenditures and conditions mapping used to prepare the french social security funding act and the public health act. *Med Care* 2022;60:655–64. <https://doi.org/10.1097/MLR.0000000000001745>.
- [18] Drézen E, Happe A, Kerbrat S, Balusson F, Oger E. New metrics for assessing linkage quality in deterministic record linkage of health databases; 2022. <https://hal.science/hal-03601245> [accessed January 21, 2024].
- [19] French National Authority for Health (HAS). Choices in methods for economic evaluation – HAS; 2020. https://www.has-sante.fr/upload/docs/application/pdf/2020-11/methodological_guidance_2020_-_choices_in_methods_for_economic_evaluation.pdf. [accessed January 21, 2024].
- [20] Black WC. The CE plane: a graphic representation of cost-effectiveness. *Med Decis Mak Int J Soc Med Decis Mak* 1990;10:212–4. <https://doi.org/10.1177/0272989X9001000308>.
- [21] Fenwick E, Marshall DA, Levy AR, Nichol G. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC Health Serv Res* 2006;6:52. <https://doi.org/10.1186/1472-6963-6-52>.
- [22] Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves—facts, fallacies and frequently asked questions. *Health Econ* 2004;13:405–15. <https://doi.org/10.1002/hec.903>.
- [23] Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Value Health J Int Soc Pharmacoecon Outcomes Res* 2022;25:3–9. <https://doi.org/10.1016/j.jval.2021.11.1351>.
- [24] Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. *Lancet Glob Health* 2023;11:e833–42. [https://doi.org/10.1016/S2214-109X\(23\)00162-6](https://doi.org/10.1016/S2214-109X(23)00162-6).
- [25] Avgousti R, Antypas C, Armpilia C, Simopoulou F, Liakouli Z, Karaiskos P, et al. Adaptive radiation therapy: when, how and what are the benefits that literature provides? *Cancer Radiother J Soc Francaise Radiother Oncol* 2022;26:622–36. <https://doi.org/10.1016/j.canrad.2021.08.023>.
- [26] Chauhan AS, Prinja S, Ghoshal S, Verma R. Cost-effectiveness of treating head and neck cancer using intensity-modulated radiation therapy: implications for cancer control program in India. *Int J Technol Assess Health Care* 2020;36:492–9. <https://doi.org/10.1017/S0266462320000677>.
- [27] Clark EE, Thielke A, Kriz H, Bunker K, Ryan K, Liu R, et al. Intensity modulated radiation therapy. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University; 2012.
- [28] Kohler RE, Sheets NC, Wheeler SB, Nutting C, Hall E, Chera BS. Two-year and lifetime cost-effectiveness of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2013;87:683–9. <https://doi.org/10.1016/j.ijrobp.2013.08.011>.
- [29] Li G, Xia Y-F, Huang Y-X, Okat D, Qiu B, Doyen J, et al. Optimizing oropharyngeal cancer management by using proton beam therapy: trends of cost-effectiveness. *BMC Cancer* 2021;21:944. <https://doi.org/10.1186/s12885-021-08638-2>.
- [30] Sher DJ, Tishler RB, Pham N-L, Punglia RS. Cost-effectiveness analysis of intensity modulated radiation therapy versus proton therapy for oropharyngeal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2018;101:875–82. <https://doi.org/10.1016/j.ijrobp.2018.04.018>.
- [31] Varmaghani M, Amiri M, Ebrahimipour H, Salek R, Javan-Noughabi J. The cost effectiveness of intensity-modulated radiation therapy and three-dimensional conformal radiation therapy in the treatment of head and neck cancers. *Radiat Oncol Lond Engl* 2023;18:138. <https://doi.org/10.1186/s13014-023-02327-z>.
- [32] Yong JHE, Beca J, O'Sullivan B, Huang SH, McGowan T, Warde P, et al. Cost-effectiveness of intensity-modulated radiotherapy in oropharyngeal cancer. *Clin Oncol R Coll Radiol G B* 2012;24:532–8. <https://doi.org/10.1016/j.clon.2012.05.010>.
- [33] Kazibwe J, Gheorghe A, Wilson D, Ruiz F, Chalkidou K, Chi Y-L. The use of cost-effectiveness thresholds for evaluating health interventions in low- and middle-income countries from 2015 to 2020: a review. *Value Health J Int Soc Pharmacoecon Outcomes Res* 2022;25:385–9. <https://doi.org/10.1016/j.jval.2021.08.014>.
- [34] Bessou A, Colin X, De Nascimento J, Sopwith W, Ferrante S, Gorsh B, et al. Assessing the treatment pattern, health care resource utilisation, and economic burden of multiple myeloma in France using the Système National des Données de Santé (SNDS) database: a retrospective cohort study. *Eur J Health Econ HEPAC Health Econ Prev Care* 2023;24:321–33. <https://doi.org/10.1007/s10198-022-01463-9>.
- [35] Daval L, Nze Ossima A, Clément M-C, Michel M, Chevreur K. Estimation of the width of uncertainty in care consumption and costs when using common data collection tools in economic evaluations: a benchmark for sensitivity analyses. *Value Health J Int Soc Pharmacoecon Outcomes Res* 2021;24:1416–22. <https://doi.org/10.1016/j.jval.2021.05.004>.
- [36] Briggs AH, O'Brien BJ. The death of cost-minimization analysis? *Health Econ* 2001;10:179–84. <https://doi.org/10.1002/hec.584>.
- [37] Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health J Int Soc Pharmacoecon Outcomes Res* 2015;18:161–72. <https://doi.org/10.1016/j.jval.2015.02.001>.
- [38] Dakin H, Wordsworth S. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. *Health Econ* 2013;22:22–34. <https://doi.org/10.1002/hec.1812>.
- [39] Defourny N, Monten C, Grau C, Lievens Y, Perrier L. Critical review and quality-assessment of cost analyses in radiotherapy: how reliable are the data? *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2019;141:14–26. <https://doi.org/10.1016/j.radonc.2019.09.020>.
- [40] Defourny N, Perrier L, Borrás J-M, Coffey M, Corral J, Hoozée S, et al. National costs and resource requirements of external beam radiotherapy: a time-driven activity-based costing model from the ESTRO-HERO project. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2019;138:187–94. <https://doi.org/10.1016/j.radonc.2019.06.015>.
- [41] Parikh NR, Clark MA, Patel P, Kafka-Peterson K, Zaidé L, Ma TM, et al. Time-driven activity-based costing of CT-guided vs MR-guided prostate SBRT. *Appl Radiat Oncol* 2021;10:33–40.
- [42] Borrás JM, Corral J, Aggarwal A, Audisio R, Espinas JA, Figueras J, et al. Innovation, value and reimbursement in radiation and complex surgical oncology: time to rethink. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2022;169:114–23. <https://doi.org/10.1016/j.radonc.2021.08.002>.
- [43] Borrás JM, Lievens Y, Coll C, Denjoy N, Espinàs JA, Figueras J, et al. Tackling reimbursement for radiation oncology and cancer surgery: challenges and options; 2020.
- [44] Meeks SL, Mathews R, Mojica J, Shah AP, Kelly P, Dvorak T. Impact of radiation oncology alternative payment model on community cancer centers. *JCO Oncol Pract* 2021;17:e1949–57. <https://doi.org/10.1200/OP.21.00298>.