

## Cost of Squamous Cell Cancer of the Head and Neck

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### ABSTRACT

**Objectives:** The costs of diagnostic, treatment, and end-of-life phases for advanced squamous cell carcinoma of the head and neck (SCCHN) are unknown, particularly after the approval of the first biologic agent for treatment, cetuximab. We aimed to characterize costs for each of the 3 disease phases and total cost of care for patients with advanced SCCHN before and after the approval of cetuximab.

**Study Design:** Retrospective, observational, cohort study.

**Methods:** This was a retrospective analysis of the PharMetrics Choice insurance claims database. Patients 20 years or older with *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes suggestive of advanced SCCHN between March 1, 2003, and March 1, 2008, were included. Patients were divided into 2 cohorts by date of diagnosis: a “prebiologic” period and a “postbiologic” period. Descriptive statistics were used to summarize baseline patient characteristics, monthly and total medical costs, and cost drivers. The Mann-Whitney U test was used to compare medical costs between segments and cohorts.

**Results:** A total of 365 patients with SCCHN met the study criteria. Median monthly medical costs were: diagnosis (\$2199), treatment (\$4161), end-of-life (\$6614), and total (\$4167). Total medical costs were driven primarily by outpatient costs (23%), inpatient costs (18%), and the cost of radiation therapy (16%). In the treatment segment, median monthly costs were significantly lower in the prebiologic era compared with the postbiologic era (\$3301 vs \$4381;  $P = .0024$ ).

**Conclusions:** Median total costs exceeded \$4000 per month for patients with SCCHN, driven primarily by the end-of-life segment. The median monthly costs of the treatment segment increased by approximately \$1000 following cetuximab’s approval.

*Am J Pharm Benefits.* 2017;9(3):89-94

Head and neck cancers account for approximately 3% of all cancer diagnoses and 2% of cancer-related deaths in the United States.<sup>1</sup> In 2015, an estimated 45,780 Americans were diagnosed with head and neck cancers, of which 90% were of squamous cell histology.<sup>1-3</sup> Currently, the estimated 5-year survival rate for all patients diagnosed with squamous cell carcinoma of the head and neck (SCCHN) is 60%. Of those diagnosed with SCCHN, 60% are diagnosed with locally or regionally advanced disease, generally denoting a poorer prognosis.<sup>1,4,5</sup> Fortunately, recent data from the American Cancer Society demonstrate a steady annual decrease in SCCHN mortality of approximately 2% for women. Mortality in men has since stabilized.<sup>1</sup>

The decrease in mortality is likely attributable to advances in the management of head and neck cancers.<sup>1</sup> The National Comprehensive Cancer Network clinical practice guidelines recommend combined modality therapy for patients diagnosed with locally or regionally advanced disease. Currently, first-line recommendations include combining radiation therapy with chemotherapy (eg, cisplatin) or with biologic therapy.<sup>5</sup> Cetuximab is a biologic therapy, an epidermal growth factor receptor inhibitor approved in 2006 for use in patients with locally or regionally advanced SCCHN in combination with radiation therapy.<sup>6-8</sup> Second-line options include surgery, radiation (if not previously given), or systemic therapy with various single-agent chemotherapeutic options: cisplatin, carboplatin, docetaxel, cetuximab, or fluorouracil.<sup>5</sup>

With the rising cost of cancer care in the United States, new therapies must be critically evaluated in regard to their economic value. Multiple factors, including extent of care, advancements in diagnostic capabilities, and increases in cancer prevalence rates, have contributed to this rise in recent years.<sup>9-11</sup> The growing use of newer drug therapies, such as biologic agents, is often cited as one of the primary drivers of increasing cancer costs.<sup>10,12</sup> However, available cost analyses of head and neck cancers have been limited to time periods preceding approval of these newer treatment modalities.<sup>13,14</sup>

## PRACTICAL IMPLICATIONS

- The cost of squamous cell cancer of the head and neck (SCCHN) is driven primarily by end-of-life care and outpatient costs.
- Monthly treatment costs increased after the approval of cetuximab.
- The study findings provide awareness of the costs of SCCHN care among commercial payers.
- The study can help drive discussions related to containing costs and evaluating treatments during SCCHN end-of-life care.

Differing patterns of care across disease segments (ie, diagnosis, treatment, end-of-life) make it difficult to quantify the costs of managing specific cancers<sup>5,15-18</sup>; however, a longitudinal evaluation of incidence-based direct medical costs for specific cancers can be used to estimate long-term costs for managing patients with cancer.<sup>19</sup> The objective of this study was to describe the segmented (diagnosis, treatment, end-of-life) and total direct medical costs associated with the management of SCCHN.

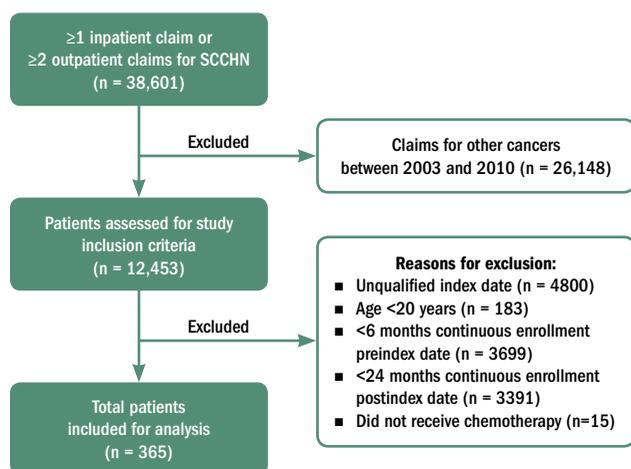
## METHODS

This was a retrospective, observational, cohort study utilizing data from a private payer claims database (PharMetrics Choice) spanning the period from September 1, 2002, through March 1, 2010. The study was approved by the institutional review board at the University of Texas Health Science Center at San Antonio.

### Data Source

The PharMetrics database is an integrated patient-level database of pharmacy and medical claims from more than 90 commercial health plans in the United States. The

**Figure 1.** Summary of Patient Population Inclusion



SCCHN indicates squamous cell carcinoma of the head and neck.

database is representative of commercially insured patients across the United States and captures various claims rendered, such as laboratory and diagnostic tests, outpatient physician visits, hospitalizations, outpatient clinic visits, and pharmacy-related costs. The PharMetrics Choice database (derived from the PharMetrics database) excludes claims for carve-outs,

patients who lack integrated pharmacy and medical benefits, plans that have failed to submit data for the previous 2 years, and plans that lack membership tables. In 2010, more than 55 million patients were included in the PharMetrics Choice database.

### Study Design

All patients 20 years or older and enrolled in an eligible health plan for more than 1 day between March 1, 2003, and March 1, 2008, (the enrollment period) were considered for initial sampling. Individuals with advanced or locally advanced SCCHN were identified using an algorithm developed for use with healthcare claims data (FIGURE 1).<sup>20,21</sup> Diagnosis of new SCCHN cases was determined by the presence of at least 1 inpatient or 2 outpatient claims suggestive of head and neck malignancies at sites with a high proportion of squamous cell histology. These claims were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 140.X to 148.X, 161.X, 195.0, and 196.0. The date of the first claim for SCCHN was assigned as the index date. Eligible patients were required to have 6 months of continuous enrollment preindex date and 24 months of continuous enrollment postindex date to account for patient progression through all segments of disease. Additionally, patients were required to have claims and procedure codes indicative of receipt of therapy for squamous cell histology and recurrent and/or advanced disease (ie, stage II, III, IV). Patients with another primary malignancy, as evidenced by at least 1 inpatient or 2 outpatient claims, were excluded.

Variables evaluated at the time of the index date included patient age, sex, geographic region, and National Cancer Institute (NCI) Comorbidity Index score. This score was derived from the Charlson Comorbidity Index and numerically represents the risk of impending mortality according to the presence of various chronic diseases at the time of cancer diagnosis.<sup>22</sup> Additional data, such as race, ethnicity, tobacco and alcohol use, and human papilloma virus status, were not reported for the study population due to a lack of reporting of such information in the claims database.

## Disease Segments

Patients were followed from the index date until patient death, end of continuous enrollment, or end of the study period (March 1, 2010). Patient follow-up was evaluated in total and as segments (ie, diagnosis, treatment, and end-of-life). These 3 disease segments were derived from prior published studies evaluating the economic burden of cancer across phases of care.<sup>16-18</sup>

The diagnosis segment was defined as the period 90 days immediately preceding the index date plus the time until the receipt of active treatment, identified as claims for surgery, radiation therapy, biologic therapy, or chemotherapy. The treatment segment consisted of all claims identified following the initiation of active treatment until the study's end or the start of the end-of-life segment. The end-of-life segment was defined as the period 90 days preceding death.

As reporting of mortality in healthcare claims is limited, we used a previously published algorithm for identifying deaths within insurance claims databases.<sup>16-18,23</sup> Patients with claims ending prior to the study end (March 1, 2010) and coding of a “likely fatal event” (eg, hospitalization, hospice, emergency department [ED], resuscitation, or cardiac arrest) within 30 days of the last date of active enrollment were considered to have died. Those patients who did not experience a likely fatal event during the study period would have remained in the treatment phase and not experienced the end-of-life phase.

## Outcomes

The primary outcome was direct medical costs of SCCHN from the payer perspective, according to the specific disease segment: diagnosis, treatment, and end-of-life. Cost estimates were based on direct medical costs paid and included total reimbursed amounts and all paid medical and pharmacy claims. Claims for hospitalization, ED visits, outpatient physician visits, outpatient treatments, skilled nursing care, hospice direct costs, radiation therapy, and drug costs made during the follow-up period were included. Costs were reported as monthly costs for each segment. Secondary outcomes included total monthly cost, cost per disease segment and total cost, percentage of costs for individual claims, and cost comparison among the prebiologic and postbiologic cohorts.

The approval of new treatments allowed stratification across 2 time periods. Patients were categorized into cohorts surrounding the approval of the biologic agent, cetuximab. Patients with an index date between March 1, 2003, and February 28, 2006, were assigned to the prebiologic cohort whereas patients with an index date on or following March 1, 2006, were assigned to the postbiologic cohort.

**Table 1.** Duration and Cost According to Segment of Disease

Variable	Overall (n = 365)	Diagnosis (n = 365)	Treatment (n = 365)	End-of-Life (n = 44)
Median follow-up, months	30.1	2.8	27.3	2.9
Median total cost, \$	110,793	6341	99,247	18,390
Median monthly cost, \$	4167	2199	4161	6614

Costs were compared among individuals according to prespecified cohort.

Additionally, those patients who experienced all segments of care (ie, diagnosis, treatment, and end-of-life) were assessed separately. This analysis was performed to evaluate costs incurred in patients with a likely fatal event, as these costs may differ from those for patients experiencing only the first 2 of the 3 segments of care associated with advanced SCCHN. These patients were referred to as the “full-care” group.

## Statistical Analysis

Categorical data were reported as numbers and percentages. Data were compared using the  $\chi^2$  method. Continuous data were reported using descriptive methods and compared across cohorts using the Mann-Whitney U test. All costs were adjusted to 2009 US dollars based on the medical services component of the Consumer Price Index and were presented as medians and interquartile ranges (IQRs).

All statistical analyses were conducted using JMP version 9.0 (SAS Corporation; Cary, North Carolina).

## RESULTS

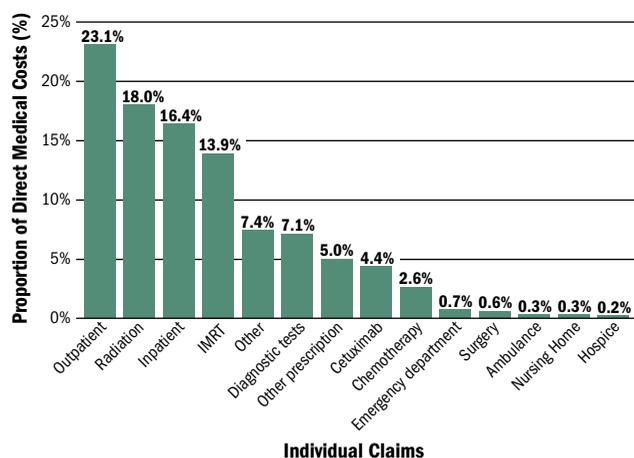
### Patient Demographics

Initial sampling identified 38,601 patients with head and neck malignancies. A total of 365 patients met the study inclusion criteria for SCCHN: 100 in the prebiologic period and 265 in the postbiologic period (Figure 1). The **EAPPENDIX** (available at [www.ajpb.com](http://www.ajpb.com)) describes patient demographics for the study population in composite and among the prebiologic and postbiologic cohorts. Patients were predominately male (78%), with a median age of 57 years. The mean NCI Comorbidity Index score was 0.53 (SD = 1.04).

### Direct Medical Costs

The median duration of follow-up after the index date for all patients with SCCHN was 30.1 months (eAppendix), predominated by the treatment segment (median = 27.3 months). Overall, the total median cost incurred for patients with SCCHN was \$110,793 (IQR, \$73,769-\$156,836) (**TABLE 1**). The median cost for care of patients with SCCHN incurred in this study was \$4167 per month over the follow-up period. The end-of-life segment was associated with the

**Figure 2.** Treatment Modalities as a Proportion of Total Treatment Costs



IMRT indicates intensity-modulated radiation therapy.

highest monthly cost (median = \$6614; IQR, \$3172-\$17,158), followed by the treatment segment (median = \$4161; IQR, \$2540-\$7915); however, total costs (median = \$99,247; IQR, \$63,117-\$142,653) were highest in the treatment segment due to the longer duration of follow-up. The diagnostic segment incurred the lowest total (median = \$6341; IQR, \$2749-\$11,121) and monthly (median = \$2199; IQR, \$1077-\$4677) costs.

Outpatient clinic visits, radiation, and inpatient therapy costs were the 3 main cost drivers, representing 23%, 18%, and 16% of total medical costs, respectively. During the treatment segment, outpatient visits (23%) were the primary cost driver (FIGURE 2). Radiation therapy, when combined with intensity-modulated radiation therapy (IMRT), accounted for 39.5% of the total costs incurred. Composite oncology drug (chemotherapy plus cetuximab) claims accounted for 7% of treatment costs, with chemotherapy accounting for 2.6% and biologics 4.4%. Surgery accounted for only 0.6%.

### Prebiologic Versus Postbiologic Cohorts

Patient characteristics were similar for prebiologic and postbiologic cohorts, with the exception of geographic

region ( $P < .0036$ ) (eAppendix). The overall duration of diagnostic and end-of-life segments (if present) were similar, with median durations of 2.8 and 2.9 months, respectively (TABLE 2). Patients in the prebiologic period had a significantly longer median duration of treatment, resulting in a longer observation period compared with the postbiologic period (29.1 vs 26.8 months;  $P = .0023$ ). Median monthly costs in the treatment segment were increased in the postbiologic cohort compared with the prebiologic cohort (\$3301 vs \$4381;  $P = .0024$ ), whereas costs in the diagnostic and end-of-life segments were not statistically different (Table 2). Total monthly costs were higher in the postbiologic cohort compared with the prebiologic cohort (\$3236 vs \$4421;  $P = .0006$ ). Medical claims between cohorts remained unchanged, with the exception of IMRT (8% vs 14%;  $P < .0001$ ), chemotherapy (4% vs 2%;  $P = .001$ ), and cetuximab (0% vs 4%;  $P < .0001$ ) use.

### Full-Care Group Analysis

Twelve percent of patients ( $n = 44$ ) in this study were included in the full-care group: 14 prebiologic patients and 30 postbiologic patients. Baseline characteristics of patients in the full-care group were similar to patients in the non-full-care group: median age (58.5 vs 57 years;  $P = .0943$ ), percentage male (81.8% vs 77.8%;  $P = .5521$ ), and mean NCI comorbidity index score (0.73 vs 0.50;  $P = .1476$ ). Full-care patients in the prebiologic and postbiologic cohorts had similar baseline characteristics.

Median monthly costs in the full-care group according to segment were: diagnostic segment (\$1733; IQR, \$660-\$3614), treatment segment (\$8265; IQR, \$3946-\$17,851), and end-of-life segment (\$6614; IQR, \$3172-\$17,157). Total median costs for the follow-up period were \$122,041 (IQR, \$73,582-\$168,461), with the highest proportion of costs incurred in the treatment segment (\$89,281; IQR, \$46,598-\$121,067). In comparing prebiologic and postbiologic cohorts, median monthly costs and median total costs were similar across all disease segments. The total median monthly cost for the follow-up period (\$7817;

**Table 2.** Duration and Cost Comparison by Disease Segment Across Pre- and Postbiologic Cohorts

Variable	Overall (n = 365)		Diagnosis (n = 365)		Treatment (n = 365)		End-of-Life (n = 44)	
	Pre- (n = 100)	Post (n = 265)	Pre- (n = 100)	Post (n = 265)	Pre- (n = 100)	Post (n = 265)	Pre- (n = 14)	Post (n = 30)
Median follow-up, months	32.2 <sup>a</sup>	29.4 <sup>a</sup>	2.8	2.9	29.1 <sup>a</sup>	26.8 <sup>a</sup>	2.9	2.9
Median total cost, \$	109,405	112,117	5121 <sup>a</sup>	6860 <sup>a</sup>	101,037	98,111	15,854	21,822
Median monthly cost, \$	3236 <sup>a</sup>	4421 <sup>a</sup>	2042	2504	3301 <sup>a</sup>	4382 <sup>a</sup>	6108	10,380

<sup>a</sup>Indicates  $P < .05$  for the prebiologic cohort compared with the postbiologic cohort.



IQR, \$4053-\$12,243) was higher compared with the non–full care group, (\$3889; IQR, \$2549-\$6757;  $P = .0002$ ).

## DISCUSSION

To our knowledge, this is the first study to characterize the segmented direct medical costs of SCCHN across disease segments during the era of biologic therapy. The results of this study illustrate the economic impact of SCCHN across different segments of care and capture the impact of cetuximab by evaluating the time surrounding the approval of this agent.

Earlier studies evaluated the cost of head and neck cancers utilizing data from the 1990s.<sup>13,14</sup> In a study by Lang et al, the economic cost of SCCHN in patients 65 years or older used data collected from the Surveillance, Epidemiology, and End Results database.<sup>13</sup> The study results demonstrated a significant increase in the median cost of SCCHN compared with controls (\$1428 vs \$446 per month;  $P < .001$ ), with most costs incurred from hospitalization. The investigators found that patients with regional and distant disease had higher average costs (\$2059-\$2547); however, chemotherapy and radiation accounted for only 8% and 10% of regional and distant disease costs, respectively.<sup>13</sup> In comparison, the median cost of care of patients with SCCHN incurred in this study was \$4167 per month over the follow-up period. When converted to 2009 dollars, the median cost per month incurred for advanced-stage disease in the study by Lang et al<sup>13</sup> would be approximately \$3300, which is comparable with the costs incurred in our study.

Although our study is the first to our knowledge to evaluate the segmented costs of SCCHN, other studies have conducted similar analyses in other malignancies.<sup>16-18</sup> Song et al evaluated the costs incurred for metastatic colorectal cancer during the era of biologic therapy.<sup>17</sup> In this study, the cost for managing colorectal cancer was driven primarily by the costs incurred during the end-of-life phase. Other studies in breast and colorectal cancer have shown similar findings, with diagnosis costs consistently exceeding treatment costs.<sup>16-18</sup> In our study, the costs associated with managing SCCHN were driven by both treatment and end-of-life segment costs when evaluating those patients who experienced a likely fatal event (full-care group).

Unlike previous studies evaluating segments of care, we defined the treatment segment as beginning with the first claim for any active treatment. Previous studies have defined the diagnosis segment strictly as the first 3 months following the index date, meaning that active treatment-related costs given early in the management of the disease would be included under the diagnosis-segment costs. This difference in defining segments may contribute to the

higher costs seen during the treatment segment in our study compared with other studies that have found treatment costs to be the least costly of the 3 phases.

We found that the median costs per month were higher in the postbiologic cohort compared with the prebiologic cohort, driven by cost differences during the treatment segment. This variation in costs may be attributable to changes in treatment practice. In addition to the approval and use of cetuximab, we noted a change in the use of IMRT and chemotherapy: the use of IMRT between the prebiologic and postbiologic cohorts nearly doubled, whereas the costs attributable to chemotherapy decreased. These changes in treatment practice likely affected treatment-phase costs and, subsequently, overall costs in this study.

Our findings demonstrating increasing SCCHN costs following the approval of cetuximab help to highlight the importance of new medication approvals in oncology and the costs associated with these new therapies. Of importance, our study results reveal that the increasing cost of cancer care is not only driven by medication costs, but rather, is multifactorial. Additionally, our study highlights that cost-of-care trends across different segments of care vary, and further studies evaluating cost drivers should be conducted to identify areas of opportunity to curb cost.

## Strengths and Limitations

Our study is strengthened by the use of data from a large integrated healthcare claims database representative of all regions in the United States. By defining the segments of care to include the time prior to the initial diagnosis date, diagnostic tests and procedures could be captured to ascertain more accurate assessments of diagnostic costs. Additionally, we are better able to assess all therapy-related costs as treatment-segment costs by defining the treatment segment to begin with the first claim for active therapy. In addition, the determination of cost estimates helped to account for variability between patients, such as age and follow-up time.

Despite the novelty and strengths of this study, it also has limitations. Limitations to the use of administrative claims databases for health economic research have been previously described.<sup>24</sup> Lack of diagnostic or histologic confirmation of SCCHN and the reliance on *ICD-9-CM* codes may have led to errors in defining our cohort. This would also lead to the inclusion of patients with different disease stages and treatments, which might limit the generalizability of the results to individual patients. The algorithms used in this study to identify patients with SCCHN, as well as likely fatal events, have also not been validated. Additionally, the distinction between recurrent and newly diagnosed SCCHN

may lead to the underestimation of diagnostic costs due to fewer diagnostic tests being utilized for those patients with recurrent disease. Certain patient, clinician, or treatment factors that were not accounted for in our study design might contribute to differences in costs between groups.

Next, the exclusion criteria resulted in a relatively small sample size that might not have been adequately powered to identify statistically significant differences in outcomes between all groups, particularly in the smaller end-of-life and full-care groups. The small sample of the full-care group, in particular, might limit the generalizability of the costs described in this study to all patients with SCCHN once they have experienced all 3 segments of the disease. Next, a proxy for mortality was utilized to help identify information on death, as mortality is not recorded within the PharMetrics database.

Lastly, this study was designed to describe the overall costs associated with SCCHN and was unable to account for neither concurrent changes in health outcomes nor changes in the proportion of SCCHN patients who receive cetuximab. Increased use of cetuximab or other therapies in recent years could result in different overall SCCHN costs.

## CONCLUSIONS

Median total costs exceeded \$4000 per month for patients with SCCHN; higher costs were incurred during the treatment and end-of-life segments. Outpatient and all-type radiation (conventional radiation and IMRT) costs made up the largest proportion of total medical costs incurred. The median monthly cost for the treatment segment increased by approximately \$1000 after the approval of cetuximab. <sup>ajpb</sup>

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**Source of Funding:** Bristol-Myers Squibb, Princeton, NJ.

**Author Disclosures:** Dr Frei has received research grant funding from Bristol-Myers Squibb, Forest, Pfizer, and Pharmacyclics. The remaining authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

**Authorship Information:** Concept and design (IAR, BLF, CRF, JMK); acquisition of data (JMK); analysis and interpretation of data (IAR, KRR, BLF, CRF, JMK); drafting of the manuscript (IAR); critical revision of the manuscript for important intellectual content (KRR, BLF, CRF, JMK); statistical analysis (IAR, KRR, CRF); obtaining funding (JMK).

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**eAppendix. Patient Baseline Characteristics**

<b>Characteristic</b>	<b>Overall (n = 365)</b>	<b>Prebiologic Cohort (n = 100)</b>	<b>Postbiologic Cohort (n = 265)</b>	<b><i>P</i></b>
Median age, years (IQR)	57 (51-64)	56 (51-64)	57 (52-64)	.828
Male, %	78.4	77.0	78.9	.699
Geographic region, %				
East	24.7	26.0	24.2	.004
Midwest	29.9	40.0	26.0	
South	18.9	8.0	23.0	
West	26.6	26.0	26.8	
Comorbidity score, mean ± SD	0.53 ± 1.04	0.46 ± 0.99	0.55 ± 1.05	.237
Median follow-up, months (IQR)	30.1 (16.0-39.0)	32.2 (16.9-55.4)	29.4 (15.7-37.1)	.002

IQR indicates interquartile range.