

# Oropharynx squamous cell carcinoma in Madeira population from 2009-2019: A 5 year survival analysis and predictive factors of outcome

## Original Article

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### Abstract

**Introduction:** Oropharynx squamous cell carcinoma (OP-SCC) had an annual global incidence of 98 412 and 48 143 deaths worldwide in 2020. The prognosis is variable and prognostic factors are important in selection of best treatment strategy for each patient.

**Objective:** The aim of this work was to perform a survival analysis and to investigate the impact of clinical factors on the prognosis of oropharyngeal squamous cell carcinoma (SCC) patients.

**Material and methods:** Retrospective study between 2009-2019 in a tertiary care center. Categorical data were analyzed using the exact chi-square test. The survival curves for each variable were estimated using the Kaplan-Meier method; The Cox regression model was applied to assess the effect of the clinical variables on survival (age, gender, tobacco and alcohol consumption, tumor location, prognostic stage group and type of treatment). Patients lost to follow-up or with palliative intent were excluded from the survival analysis (n=24). It was not possible to obtain HPV status.

**Results:** Data from 180 patients diagnosed with oropharyngeal squamous cell carcinomas (SCC) were analyzed.

The median age on presentation was 56,00±10,436 years and 91,9% of patients were male. The majority of patients (76,6%) reported tobacco and/or alcohol consumption. Most of the oropharyngeal SCC (88,4%) patients were diagnosed at advanced stages. 71,7% of cases were stage IV and 16,7% were stage III. The median follow-up time was 11,00 months (+/- 20,50).

In general, the only variables with a statistically significant impact on survival were tumor stage (p=0,018) and type of treatment (p<0,0001). Stage I patients had a 5-year OS rate of 56,3% while stage IV (IVa, IVb, IVc) patients had lower rates (30,6%). Regarding type of treatment, surgery alone had a 5-year overall survival rate of 46,7%, followed by surgery plus adjuvant radiotherapy (37,5%) and chemoradiotherapy (15,4%).

Amongst all the variables included in the Cox

regression model, type of treatment was the only one with a significant effect on survival: patients that underwent medical treatment alone had a 1,85 times higher death risk ( $p=0,017$ ).

Discussion and conclusion: Prognostic stage groups and type of treatment were associated with an impact on outcome, regardless of other variates, following the trend in literature.

Furthermore, medical treatment alone was also associated with lower survival rates than surgery +/- adjuvant therapy.

Keywords: oropharynx squamous cell carcinoma; staging; survival rate, surgical treatment; adjuvant therapy; medical treatment alone

## Introduction

The global incidence of oropharyngeal squamous cell carcinoma (SCC) was 98,412 in 2020<sup>1</sup>, and the incidence has increased in Europe in recent years<sup>2</sup>. Tobacco and alcohol consumption and human papilloma virus (HPV) infection are the established risk factors. The treatment options include surgery, radiotherapy, and chemotherapy, with the tumor stage and localization and patient performance status determining the choice of the therapeutic regimen. Recent studies have revealed that chemotherapy and radiotherapy are associated with significant comorbidities, such as dysphagia, osteoradionecrosis, and pharyngeal stenosis, which may be associated with increased mortality rates.<sup>3,4</sup>

Conversely, the improvement in surgical techniques via the use of CO<sub>2</sub> laser, robotic surgery, and the possibility of performing free grafting has decreased the morbidity/mortality associated with surgery, thus affording favorable oncological outcomes with increased survival in certain cases.<sup>5</sup>

Regarding patient prognosis, a Danish study reported a 5-year survival rate of 50% for oropharyngeal tumors.<sup>6</sup> In turn, an analysis pertaining to the real-world experience in the US in 2002–2006 reported a 5-year survival rate of 42.2%.<sup>7</sup> Currently, according to the data published by the American Cancer Society, the 5-year survival rate of oropharyngeal carcinomas is approximately 50%.

Regarding the factors that affect patient survival, the results of previous studies have been heterogeneous. According to a study by

Moro *et al.*, factors such as age, sex, ethnicity, and the histological grade do not affect patient survival.<sup>8</sup> However, some studies have claimed that male sex, the specific topography of the lesion, and tumor stage are negative and independent prognostic factors.<sup>9,10</sup> França *et al.* identified the following factors associated with a poor prognosis: stage III/IV tumors, p-16-negative status, and time from diagnosis to the onset of treatment greater than 4 weeks.<sup>11</sup> In cases of advanced oropharyngeal tumors (T4a), Psychogios *et al.* found that cervical metastasis, perinodal invasion, and HPV-negative status were associated with lower survival rates.<sup>12</sup> Furthermore, it was demonstrated that in patients with a diagnosis of advanced oropharyngeal SCC, first-line surgical treatment was associated with a better outcome in terms of survival.<sup>12</sup>

We aimed to perform a demographic study of the population diagnosed with oropharyngeal carcinoma at Madeira Island between 2009 and 2019. Moreover, survival analysis was performed to investigate the impact of different clinical variables on the prognosis of these patients.

## Materials and Methods

A review of the clinical records was performed to identify cases of oropharyngeal SCC diagnosed and treated at the Otorhinolaryngology Service of the Hospital Central do Funchal between 2009 and 2019. A total of 180 patients with primary oropharyngeal tumors were included in the study. The mean follow-up period of these patients was 18 months; in the case of patients who were lost to follow-up, their clinical records were reviewed to determine their status (alive or deceased).

The following variables were analyzed: follow-up duration, age at diagnosis, sex, alcohol/tobacco consumption habits, topography of the lesion, extent of disease (locoregional or metastatic), tumor histological differentiation grade, stage (I, II, III, IV), and treatment modality (chemotherapy, radiotherapy, and/or surgery). Regarding alcohol consumption habits, patients who consumed more than

two units of alcoholic beverages per day were classified as having a positive drinking habit. As for tobacco use, the WHO definition of a smoker was used: "an adult who has smoked at least 100 cigarettes in their lifetime and who now smokes every day."

Staging was conducted according to the guidelines of the American Joint Committee on Cancer. Considering the study period, it was not possible to establish the HPV status for most of the patients, with all those who were tested being negative. This precluded the inclusion of this variable in the analysis.

Patients with synchronous tumors or incomplete records were excluded from this study. Patients under palliative case (n = 24) were included in the demographic study but were excluded from the survival analysis.

Categorical data were analyzed using the chi-squared test. Survival curves were estimated using the Kaplan–Meier method. The Cox regression model was applied to evaluate the effect of clinical variables on survival (age, sex, alcohol and tobacco consumption, tumor location, stage, and type of treatment). Statistical analysis was performed using the Statistical Packages for the Social Sciences software, version 25.0 (IBM Corporate, Armonk, NY, USA). Statistical significance was set at P < 0.05.

## Results

In the period between 2009 and 2019, 449 cases of head and neck oncological pathology were diagnosed at the Hospital Central do Funchal, with the prevalence of SCC being 40% (n = 180). The median follow-up time was 11 months, with a mean value of approximately 18 months.

One hundred and eighty patients with primary oropharyngeal SCC were identified, of whom 91% were men (n = 164), and 9% were women (n = 16), with a male/female ratio of approximately 10.3:1. Moreover, the mean age of the patients was 57.44 ± 10.44 years.

Regarding the risk factors, it was found that most patients (76.6%, n = 138) engaged in some type of consumption: 38.3% (n = 69)

exhibited concomitant alcohol and tobacco consumption, 29.4% (n = 53) were exclusive smokers, and 8.9% reported only alcohol consumption. A mere 12.8% of the patients (n = 23) did not smoke or drink alcohol.

Regarding the tumor topography, the most common location was the amygdala (52.2%, n = 94), followed by the base of the tongue (33.9%, n = 61). The tumor was located in the lateral wall of the oropharynx in 4.4% (n = 8) of patients and the soft palate in 2.2% (n = 4) of patients. Notably, an oropharyngeal localization was not specified in approximately 7% (n = 12) of patients.

Most of the tumors were moderately differentiated (69.4%, n = 125), whereas they were well differentiated in 6.1% (n = 11) of patients, poorly differentiated in 14.4% (n = 26) of patients, and undifferentiated in only 1.1% (n = 2) of patients.

As for the extent of the disease, 91.1% (n = 164) of patients exhibited local or locoregional disease, with only 7.8% (n = 14) having metastatic disease.

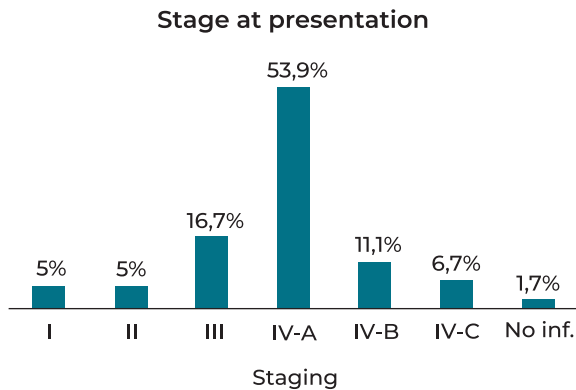
Regarding staging, it was found that 53.9% (n = 97) of the patients were in stage IVa, 11.1% (n = 20) were in stage IVb, and 6.7% (n = 12) were in stage IVc. Furthermore, 16.7% (n = 30) of patients were in stage III. A small group of patients had stage I and II disease (5% each).

Treatment with a curative intent was administered to 86.7% (n = 156) of patients. The most frequently used treatment modality was chemotherapy in conjunction with radiotherapy (49.4%, n = 89), followed by surgery with adjuvant chemoradiotherapy (CRT, 12.2%, n = 22). Moreover, 11.7% of the patients received palliative treatment (n = 21). Among the 180 patients with a diagnosis of oropharyngeal SCC, 24 were excluded from the survival analysis because they were receiving palliative treatment (n = 21) or had incomplete clinical records (n = 3).

Univariate analysis revealed that sex (P = 0.609), age (P = 0.146), tobacco/alcohol consumption habits (P = 0.269), topography/location of the lesion (P = 0.309), histological differentiation grade (P = 0.116), and extent of the disease

( $P = 0.147$ ) did not have a significant effect on the survival of patients. In turn, the only variables with a statistically significant impact

**Figure 1**  
Stage at presentation



on patient prognosis were the tumor stage ( $P = 0.018$ ) and type of treatment ( $P < 0.001$ ). Patients with stage I disease exhibited an overall 5-year survival rate of 56.3%, whereas those with stage IV (IVa, IVb, IVc) had a lower survival rate (30.6%).

Surgery alone resulted in a survival rate of 46.7%, followed by surgery in conjunction with radiotherapy (37.5%) and chemoradiotherapy (15.4%).

For a more detailed analysis, the type of treatment was divided into two categories: medical treatment alone (chemotherapy, radiotherapy, chemoradiotherapy) and

surgical treatment, alone or in combination with adjuvant therapy (surgery + chemoradiotherapy, surgery + radiotherapy, surgery). The type of treatment was then adjusted to the stage.

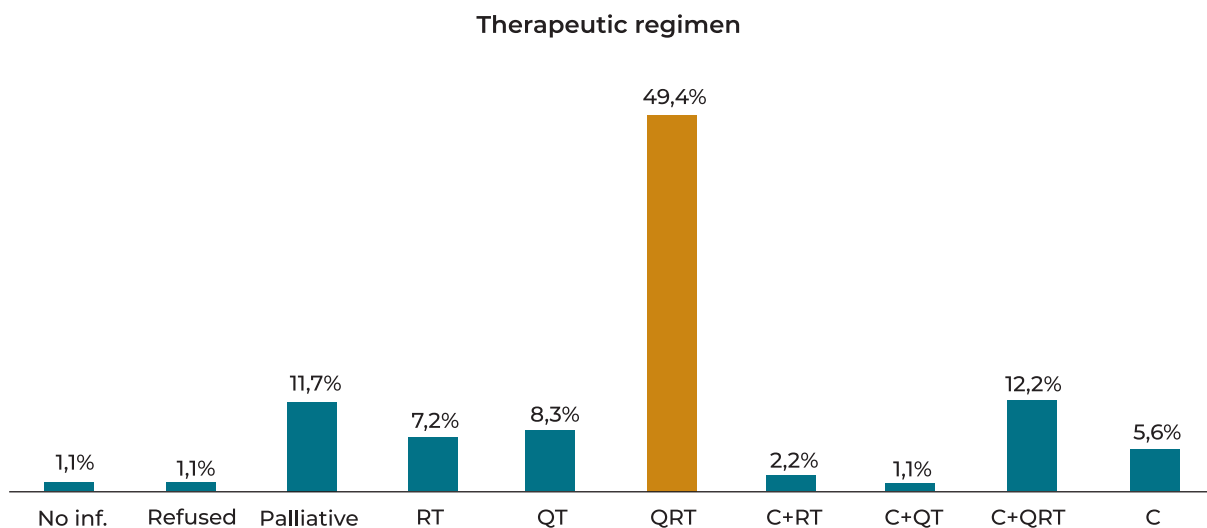
In stage I, the main treatment strategy was surgery alone or together with adjuvant therapy ( $n = 5$ , 62.5%), whereas in stage II ( $n = 5$ , 55.5%), III ( $n = 18$ , 66.7%), and IV ( $n = 90$ , 81.82%), the most frequent therapeutic approach was medical treatment alone.

Among the 90 patients with stage IV disease who underwent medical treatment exclusively, 65 received chemoradiotherapy, 10 received radiotherapy, and 15 underwent induction chemotherapy. The patients receiving induction chemotherapy died during or immediately after the treatment. Therefore, the initially proposed treatment regimen was not followed.

Conversely, among patients with stage IV disease who underwent surgical treatment with or without adjuvant therapy ( $n = 20$ ), surgery in conjunction with chemoradiotherapy was performed in 85% ( $n = 17$ ) of patients and surgery alone in 15% ( $n = 3$ ) of patients.

Survival analysis revealed no statistically significant difference in the survival of patients who underwent medical treatment exclusively versus those who received surgical treatment

**Figure 2**  
Therapeutic regimens used in this study



**Table 1**  
Distribution of the treatment regimens according to the disease stage

Disease stage		Surgery ± medical treatment		Medical treatment	
		N	N%	N	N%
I	Total	5	13,2%	3	2,6%
	S+RT	2	5,28%	-	-
	S	3	7,92%	-	-
	Rad	-	-	3	2,6%
II	Total	4	10,5%	5	4,3%
	S+RT	2	5,25%	-	-
	S	2	5,25%	-	-
	CRT	-	-	5	4,3%
III	Total	9	23,7%	18	15,4%
	S+CRT	5	13,17%	-	-
	S+RT	3	7,90%	-	-
	S	1	2,63%	-	-
	CRT	-	-	15	12,83%
	RT	-	-	3	2,57%
IV	Total	20	52,6%	90	76,9%
	S+CRT	17	44,71%	-	-
	S	3	7,89%	-	-
	CTi	-	-	15	12,82%
	CRT	-	-	65	55,54%
	RT	-	-	10	8,54%

Abbreviations : RT, radiotherapy; CT, chemotherapy; S, surgery; CRT, chemoradiotherapy; CTi, induction chemotherapy.

(with or without adjuvant treatment) in stages I, II, and III.

However, patients with stage IV disease who underwent surgical treatment with or without adjuvant treatment exhibited a better survival rate ( $P = 0.021$ ) than those who underwent medical treatment exclusively.

Among all the variables included in the Cox regression model, the type of treatment was the only factor that had an impact on patient prognosis. The mortality in patients who underwent surgical treatment with or without adjuvant medical treatment was 1.85 times lower than that in patients who underwent medical treatment exclusively (95% confidence interval [CI]: 1.12, 3.07;  $P = 0.017$ ).

## Discussion

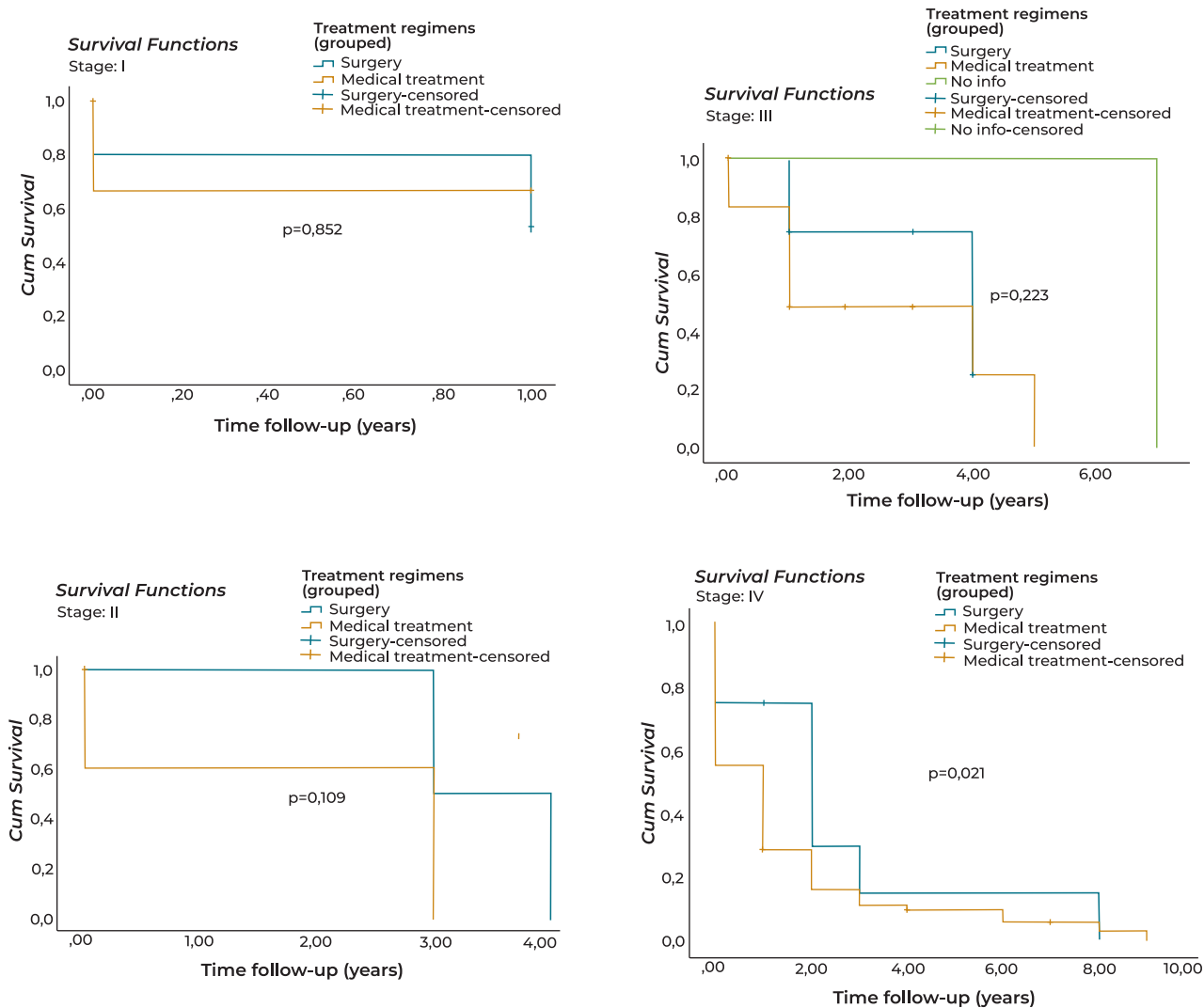
The incidence of oropharyngeal SCC has been increasing gradually. Therefore, the treatment regimens for this condition are the subject of frequent debates.

Furthermore, the factors that affect the survival of these patients were found to be heterogeneous in previous studies. However, HPV status, tumor stage, and treatment regimen are variables that have been consistently shown to have an effect on the prognosis.

In this study, similar to the results of studies published previously,<sup>8,13,14</sup> sex did not significantly affect the survival of patients, although women exhibited a tendency toward a better survival rate. Moreover, age did not

**Figure 3**

Survival curves (Kaplan–Meier method) corresponding to the treatment regimens adjusted for the tumor stage (I, II, III, and IV)



affect the survival rate, as evidenced in several other studies. Conversely, Kowalski et al. and Wagner et al. reported higher survival rates among younger patients aged <50 and <60 years, respectively.

Moreover, the tumor location and the histological differentiation grade were not found to be statistically significant prognostic factors. This finding is concurrent with the results of Moro et al., Schneider et al., and Psychogios et al.<sup>8,12,14</sup> but contradicts those of Tham et al.,<sup>15</sup> who demonstrated that oropharyngeal tumors with a location other than the amygdala and those with lower histological differentiation grades

were associated with a poorer survival rate. Regarding alcohol/tobacco consumption habits, although the literature reports direct correlation between tobacco exposure (before and after treatment) and increased risk of disease progression and death,<sup>16</sup> it was not possible to confirm this association in this study.

HPV status is one of the factors that has an effect on patient prognosis. In this study, which spanned 2009–2019, most patients were not tested for HPV; moreover, most of those tested exhibited a negative status. Therefore, it was not possible to analyze this parameter, which is one of the limitations of the study.

Among all the variables analyzed in this study, only the disease stage and treatment type had an impact on patient prognosis. In fact, patients with more advanced disease stages (stage IV), which corresponded to the majority of the cohort (71.7%), exhibited lower survival rates (30.6%) compared to patients with stage I disease (56.3%). Although this result was expected, both values were below those reported in the literature, which may have resulted from the fact that comorbidities and the performance status of the patients were not considered in this study. Moreover, the global survival rate was calculated rather than the specific disease-associated survival rate.

As for the type of treatment that was selected, a significant difference was observed between surgical treatment with or without adjuvant therapy and medical treatment alone in patients with stage IV disease exclusively: the survival rate was higher in the former ( $P = 0.021$ ). In this study, most patients included in the surgical treatment  $\pm$  adjuvant therapy group underwent surgery in conjunction with adjuvant chemoradiotherapy. Conversely, the 15 patients who received induction chemotherapy (ICT) were included in the medical treatment group, regardless of the therapeutic regimen that was applied subsequently. Nevertheless, all of these patients died after the administration of ICT, and the planned treatment regimen was not administered. Their inclusion in this group was debatable and may have resulted in a bias in the comparison of the treatment groups.

Multivariate analysis revealed that the patients in the group that underwent surgery primarily demonstrated a superior survival rate. This result agrees with the findings of Park et al.,<sup>17</sup> who exclusively included in their study patients with oropharyngeal SCC who were HPV negative or not tested, similar to the sample included in this study. They showed that surgery reduced the probability of death by 46% and decreased disease recurrence by 41%. Additionally, a study by Psychogios *et al.* compared the disease-specific survival rate between patients with stage IVa oropharyngeal

SCC who had undergone first-line surgical treatment or first-line medical treatment. The results revealed that the patients in the surgery group had a better disease-specific survival rate (52.7% vs. 31.4%,  $P = 0.001$ ).

Nevertheless, other authors did not find significant differences among the results of the various treatment groups. For example, Song et al.<sup>18</sup> analyzed a sample comprising 586 patients, among whom 419 had stage IVa oropharyngeal SCC. They did not observe any differences in the prognosis between patients treated with surgery combined with adjuvant radiotherapy and those treated with chemoradiotherapy.

## Conclusion

This study involved a demographic analysis and the evaluation of variables that affected the survival of patients diagnosed with oropharyngeal SCC at the Hospital Central do Funchal between 2009 and 2019.

The disease stage and type of treatment were found to be the significant prognostic factors. Most of the patients included in the cohort had advanced-stage disease, and as expected, patients with less-advanced disease exhibited better survival. This finding underscores the importance of early diagnosis, with the implementation of screening programs representing a potential approach to improve this reality.

Moreover, it was shown that the patients with advanced-stage disease who underwent surgical treatment combined with adjuvant medical treatment had a superior survival rate compared with those who received medical treatment exclusively. Therefore, surgery seems to play a key role in the treatment of oropharyngeal SCC.

## Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Data Confidentiality

The authors declare having followed the

protocols in use at their working center regarding patients' data publication.

### Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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### Availability of scientific data

There are no datasets available, publicly related to this work.

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