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Incidental findings during the diagnostic work-up in the head and neck cancer pathway: Effects on treatment delay and survival

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ABSTRACT

Objectives: As a result of the increasing number of diagnostic scans, incidental findings (IFs) are more frequently encountered during oncological work-up in patients with head and neck squamous cell carcinomas (HNSCC). IFs are unintentional discoveries found on diagnostic imaging. Relevant IFs implicate clinical consequences, resulting in delay in oncologic treatment initiation, which is associated with unfavorable outcomes. This study is the first to investigate the incidence and nature of IFs over the years and establish the effect of relevant IFs on delay.

Material and methods: This retrospective study compared two time periods (2010–2011 and 2016–2017), described associations between relevant IFs and delay in carepathway interval (days between first visit and treatment initiation) and assessed the effect of relevant IFs on overall two-year survival.

Results: In total, 592 patients were included. At least one IF was found in 61.5% of the patients, most frequently on chest-CT. In 128 patients (21.6%) a relevant IF was identified, resulting for the majority in radiologist recommendations (e.g. additional scanning). Presence of a relevant IF was an independent significant factor associated with delay in treatment initiation. The risk of dying was higher for patients with a relevant IF, although not significant in the multivariable model (HR: 1.46, $p = 0.079$).

Conclusion: In diagnostic work-up for HNSCC patients, relevant IFs are frequently encountered. As the frequency of additional imaging rises over the years, the number of IFs increased simultaneously. These relevant IFs yield clinical implications and this study described that relevant IFs result in significant delay in treatment initiation.

Introduction

HNSCC are relatively fast-growing tumors and most patients present with advanced disease stages [1,2]. During diagnostic work-up, the goal is adequate staging by evaluating the extent of disease and identify second primaries in order to set up an individualized treatment plan according to international guidelines.

As a result of fast tumor growth, delay in treatment initiation is associated with tumor progression, more extensive treatment and decreased overall survival [3–5]. Therefore, it is a worldwide aim to minimize the time-window in which diagnostic assessment takes place and to start treatment as soon as reasonably possible. However, no consensus on an optimal cut-off of acceptable delay exist. For instance, in the Netherlands, the guideline states that 80% of the patients has to start treatment within 30 days after first consultation (carepathway interval: CPI) in an oncological center [6]. The cut-off for CPI in Denmark is even more challenging: 22 days for initial surgery and 26 days for radiotherapy [7].

Over the years, the availability and quality of diagnostic imaging has improved, in particular regarding MRI and PET-CT [8,9]. At the same time, imaging is increasingly used by head and neck oncologists in diagnostic HNSCC work-up [10]. As a result of the increasing number of diagnostic scans, a rise in incidental findings (IFs) during oncological work-up in HNSCC seems a logical consequence; however, this has not

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been objectified yet. The incidence of IFs range between 32.0 and 86.0% [11,12]. Some of these IFs may have serious clinical consequences, such as an intervention for significant carotid artery stenosis or additional imaging to evaluate pulmonary nodules. The consequences of IFs might result in prolonged CPI and contribute to suboptimal oncological and functional outcome.

Despite the alleged increasing incidence of IFs, literature addressing the nature, etiology and clinical implications of IFs during HNSCC work-up is scarce. The effect of IFs on delay in treatment initiation has also not been described previously.

The aim of this study is therefore three folded: 1) to provide insights in the incidence, nature and implications of IFs over the years (2010–2011 vs. 2016–2017), 2) to establish the consequences of the presence of relevant IFs on delay in treatment initiation and 3) to assess the effect of IFs on two-year overall survival in patients with HNSCC.

Materials and methods

Study design and patient selection

This retrospective cohort study, performed in a tertiary oncological center, included all consecutive adult patients evaluated in either the department of head and neck surgery or oral- and maxillofacial surgery in two separate time periods. A non-WMO waiver was released with approval of the study protocol by the institutional Review Board and the protocol was prospectively registered (no. 201900818). Each patient was discussed during multidisciplinary board meetings and received treatment according to national guidelines.

Patients with a single first primary HNSCC of the oral cavity, oropharynx, hypopharynx or larynx, with first consultation between 1st of January 2010 and 31st of December 2011 (period 1) and 1st of January 2016 and 31st of December 2017 (period 2) were eligible for inclusion. These time frames were chosen to evaluate the use of imaging diagnostics and compare the subsequent incidence of IFs. Patients with palliative treatment intention, non-standard treatment or non-compliance were excluded, as were patients with synchronous second primary malignancies or patients with crucial missing data.

Data collection and definition of (relevant) incidental findings

Patient, tumor and treatment characteristics were recorded. The Union for International Cancer Control TNM Classification 7th edition was used for tumor staging [13], as it was utilized for treatment decisions in the studied time periods. Comorbidity was assessed using the Adult Comorbidity Evaluation (ACE-27), dividing patients into four categories (none, mild, moderate or severe comorbidity) [14].

In this study, incidental findings (IFs) are defined as any unintentional discovery found on diagnostic imaging, unrelated to the index tumor. IFs were identified on all imaging modalities during oncological work-up (CT, MRI, PET-CT and ultrasound) recognized by the reporting radiologist. IFs were categorized by anatomical location and etiology (any finding of possible neoplastic, inflammatory or infectious, vascular or metabolic nature). Findings resembling healed fractures or degenerative bone changes were not classified as IFs, nor were findings resembling suspect pathological lymph nodes or immediate recognition of distant metastasis, as the aim of imaging was to establish disease staging.

In order to further specify IFs and improve clinical implications of this study, relevant IFs were distinguished. IFs were considered relevant if they yielded clinical consequences (such as interventions, additional scanning or consultation of other specialists) that might impact the time-to-treatment interval. If multiple IFs were found in one patient, the (most) relevant IF was considered, based on the severity of the clinical implications, e.g. intervention > additional scanning.

Carepathway Interval (CPI) was defined as number of days between first visit in our center and treatment initiation (first day of radiotherapy or day of surgery), using a cut-off of 30 days, according to the national Dutch Head and Neck Society quality-indicator guideline [6].

Survival status (alive or deceased) was assessed two years after date of treatment initiation. Survival time was determined as the number of months between date of treatment initiation and either date of death for deceased patients or as 24 months for surviving patients.

Statistical analysis

SPSS Statistics version 23.0 (Armonk, NY: IBM Corp.) was used to analyze data. Descriptive statistics were used to compare time periods (2010–2011 vs. 2016–2017) and to depict the frequency, nature and consequences of relevant IFs. Data were presented as either means and standard deviations, medians and quartiles or absolute numbers and percentages, depending on their distribution. Correlations are calculated using Spearman's rho (ρ). Ordinal variables were compared using the χ^2 or Fisher's exact test, continuous variables (depending on their distribution) using unpaired Student's t-tests or the Mann-Whitney *U* test.

To assess the effect of relevant IFs on delay, uni- and multivariable logistic regression analyses were performed, using CPI (≥30 days) as dependent variable. Independent covariables with $p < 0.10$ in univariable analyses were included in the multivariable model. The model was checked for collinearity. Due to an evident association between number of diagnostic investigations and presence of relevant IF, only the latter was taken into account in the multivariable model.

Thirdly, cox regression analysis was performed to assess the effect of relevant IFs on two-year overall survival, establishing Hazard ratios (>1 indicating a higher risk of dying). The models were validated by checking cox proportional hazard assumptions. A two-sided $p < 0.05$ was considered statistically significant.

Results

In total, 766 patient were eligible for enrolment in this study. After applying in- and exclusion criteria (Figure 1), the final study population comprised of 592 patients (2010–2011: 306 patients, 2016–2017: 286 patients). Baseline characteristics are demonstrated in Table 1. Mean age was 65.1 years and 68.6% of the population was male.

Differences between time periods

The number of diagnostic investigations during HNSCC work-up was significantly higher in 2016–2017 compared to 2010–2011 (70.3% received > 2 diagnostic investigations, compared to 32.0% in 2010–2011, $p < 0.001$). Especially the use of MRI and PET-CT was significantly increased in 2016–2017 (Figure 2). A total of 81 (13.7%) patients (the majority with T1a laryngeal cancer) did not receive additional imaging in our center ($n = 46$ (15.0%) in 2010–2011 and $n = 35$ (12.2%) in 2016–2017.

The amount of patients starting treatment ≥ 30 days after first visit differed significantly as well: 48.0% vs. 70.3% ($p < 0.001$, for 2010–2011 and 2016–2017, respectively). Across both periods, patients with a relevant IF had significantly prolonged CPI ($p < 0.001$). The median time-to-treatment for patients with a relevant IF was 39.0 days compared to 27.0 days for patients without relevant IF in 2010–2011 ($p < 0.001$). For 2016–2017, median CPI was 39.0 days as well for patients with relevant IF, compared to 36.0 days for patients without relevant IF ($p < 0.001$). Detailed descriptive statistics of the CPI are displayed in *Supplementary Information* Table 1.

The percentage of patients presenting with stage IV disease was higher in the 2016–2017 group. Age (as continuous variable), gender, comorbidity scores, tumor site and treatment modality did not significantly differ.

Suspect pathological lymph nodes were found during diagnostic imaging in 200 patients (33.8%), with a significant decrease over time 38.2% in 2010–2011 and 29% in 2016–2017 ($p = 0.013$).

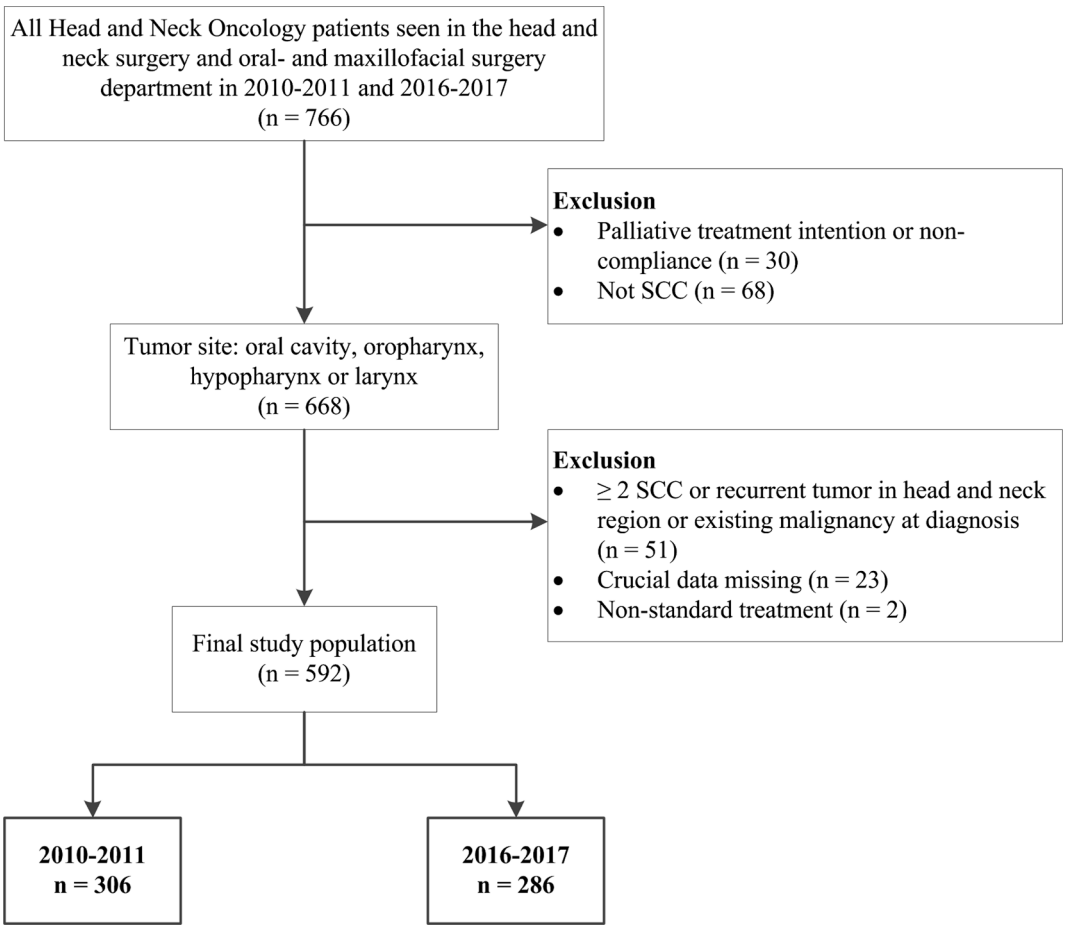

Fig. 1. Flowchart of study population, including in- and exclusion criteria.

Incidental findings

One or more IFs were found in 61.5% of the study population (Table 2). IFs were most frequently found on chest CT (Figure 2): an IF was found in 48.1% and 54.1% of the patients with a chest CT for 2010–2011 and 2016–2017, respectively. A positive correlation between the number of diagnostic investigations performed and the number of IFs was found ($\rho = 0.347$, $p < 0.001$). The percentage of IFs per imaging modality did not significantly differ over the years (Figure 2); only the total number of IFs increased in 2016–2017 as a result of a rise in performed scans.

A relevant IF was identified, in 128 patients (21.6%). Most relevant IFs consisted of miscellaneous nature, such as intrapulmonary nodules and cysts. Other findings showed benign tumors (9.4%), inflammory etiology (7.8%, e.g. non-pathological lymph nodes) or (in retrospect) synchronous primary tumors (7.0%). Most relevant IFs were found in the thorax (53.9%), followed by the head and neck region (11.7%) and abdomen (10.9%). PET-CT scanning yielded the highest percentage of relevant IFs compared to the total IFs found (65.0%). For CT-head/neck and Chest CT, the ratio was 26.2% and 37.0%, respectively. The percentage relevant IFs was 33.3% for MRI-head/neck. Ultrasonography did not result in relevant IF, the CT-venography ratio was 10%.

These relevant IFs resulted for the majority (in 60.9%) in radiologist recommendations, such as additional scanning. Other consequences yielded consultation of other specialists (7.8%), an intervention (6.3%) and a combination of these (25.0%). Nor the etiology, anatomical location or consequences did significantly differed among the two study periods.

Determinants of prolonged CPI (≥30 days)

Age, presence of suspect lymph nodes, tumor site, stage, treatment modality and presence of a relevant IF were significantly associated with a CPI ≥ 30 days in the univariable model (Table 3).

In a multivariable model, the presence of relevant IF was independently associated with delay in treatment initiation (OR: 1.879, 95%CI: 1.08–3.28, $p = 0.026$). Patients with stage III and IV disease had a 2.6 and 4.4 times significantly higher risk of CPI ≥ 30 days (95%CI: 1.21–5.42, $p = 0.014$ and 95%CI: 2.33–8.16, $p < 0.001$, respectively). Consequentially, initial treatment with radiotherapy or chemoradiation were strong independent determinants of delay (OR: 22.078, 95%CI: 10.62–45.90, $p < 0.001$ and OR: 5.142, 95%CI: 2.12–12.48, $p < 0.001$, respectively).

Overall survival

Two years after treatment initiation, overall survival was 80.7% and did not statistically differ among the two periods ($p = 0.406$). Multivariable Cox regression hazard ratios are plotted in Figure 3 (corresponding with *Supplementary* Table 2). After adjustment for age, comorbidities, tumor site, stage and initial treatment modality, the two-year overall mortality risk was 1.46 times higher for patients with a relevant IF compared to patients without relevant IFs; however this association was non-significant (HR: 1.456, 95%CI: 0.96–2.21, $p = 0.079$). If only malignancy-related IFs are taken into account, the hazard risk of dying is 2.5 times higher in a model adjusted for age, comorbidities, tumor site, stage and treatment modality (HR: 2.538, 95%CI: 1.14 to 5.65, $p = 0.022$).

Advanced disease stage, as well as moderate and severe

Table 1
Patient-, tumor- and treatment characteristics for the entire study cohort and each time period separately.

Characteristics	All (n = 592)	2010–2011 (n = 306)	2016–2017 (n = 286)	p-value
Age – years				**0.003**
≤65	294 (49.7)	170 (47.2)	124 (43.4)	
>65	298 (50.3)	136 (44.4)	162 (56.6)	
Continuous	65.1 ± 11.2	64.2 ± 11.8	66.0 ± 10.5	0.050
Gender				0.289
Male	406 (68.6)	216 (70.6)	190 (66.4)	
Female	186 (31.4)	90 (29.4)	96 (33.6)	
ACE-27				0.763
None	132 (22.6)	72 (24.0)	60 (21.1)	
Mild	249 (42.6)	124 (41.3)	125 (43.9)	
Moderate	147 (25.1)	73 (24.3)	74 (26.0)	
Severe	57 (9.7)	31 (10.3)	26 (9.1)	
Diagnostic investigation				**<0.001**
≤2 investigations	293 (49.5)	208 (68.0)	85 (29.7)	
>2 investigations	299 (50.5)	98 (32.0)	201 (70.3)	
Continuous	3 [2–4]	2 [1–3]	3 [2–4]	**<0.001**
CPI	34.00 [1–140]	29.00 [5–137]	39.00 [1–140]	**<0.001**
≥30 days	348 (58.8)	147 (48.0)	201 (70.3)	**<0.001**
With relevant IF	39.00 [1–137]	39.00 [8–137]	39.00 [1–100]	**<0.001**†
Without relevant IF	32.00 [1–140]	27.00 [5–113]	36.00 [1–140]	
Tumor site				0.067
Oral cavity	234 (39.5)	135 (44.1)	99 (34.6)	
Oropharynx	129 (21.8)	67 (21.9)	62 (21.7)	
Larynx	192 (32.4)	86 (28.1)	106 (37.1)	
Hypopharynx	37 (6.3)	18 (5.9)	19 (6.6)	
Stage of disease				**0.001**
Stage I	192 (32.5)	120 (39.2)	72 (24.2)	
Stage II	94 (15.9)	53 (17.3)	41 (14.3)	
Stage III	78 (13.2)	38 (12.4)	40 (14.0)	
Stage IV	228 (38.5)	95 (31.0)	133 (46.5)	
Treatment modality				0.267
Surgery	326 (55,1)	174(56.9)	152(53.1)	
Radiotherapy	154 (26.0)	71 (23.2)	83 (29.0)	
Chemoradiation	112 (18.9)	61 (19.9)	51 (17.8)	

All data are presented as number of cases (percentage), mean ± standard deviation or median [interquartile range]. ACE-27: Adult Comorbidity Evaluation, CPI: carepathway interval, IF: incidental finding. †CPI with relevant IF compared to CPI without relevant IF in the total study population. 2010–2011: p = 0.002, 2016–2017: p = 0.004.

comorbidities and patients with hypopharyngeal tumors were independently associated with increased overall mortality risks.

Discussion

Diagnostic imaging, as a part of the accurate evaluation of the disease, is key to establish an optimal individual treatment plan.

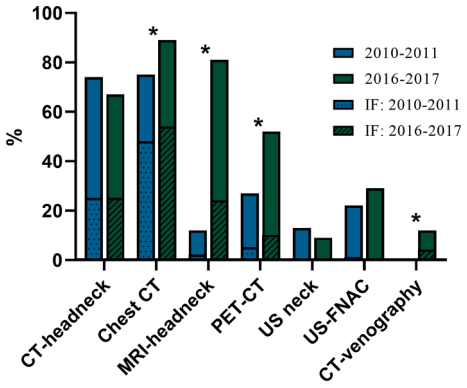

Fig. 2. Diagnostic investigations and corresponding percentage of incidental findings for 2010–2011 and 2016–2017. *indicates a significant difference comparing both periods, p < 0.05. CT: Computed Tomography. FNAC: fine-needle aspiration cytology. MRI: Magnetic Resonance Imaging. PET: Positron Emission Tomography. US: Ultrasound.

Unintended, coincidental accompanying findings during diagnostic work-up can confuse the diagnostic process.

This study is, to our knowledge, the first to describe the association between incidental findings and delay in treatment initiation as well as the effect on overall survival. IFs were commonly encountered in this study, reporting one or more IFs in 61.5% of the study population. In total, 21.6% of these IFs were considered as relevant, involving clinical implications. Over the years, a rise in diagnostic imaging performed was observed. Subsequently, the number of relevant IFs significantly increased as well (14.1% in 2010–2011 vs. 29.7% in 2016–2017).

Presence of a relevant IF was an independent factor associated with delay in start of oncological treatment (CPI ≥ 30 days). An insignificant, however, 1.46 times higher 2-years mortality risk in patients with relevant IF was found.

Incidental findings and delay in treatment initiation

The incidence of IFs has increased over the past years, presumably due to a rise in performed imaging diagnostics as well as enhanced quality of imaging techniques [10,15], in accordance with our findings comparing the two study periods. An explanation for the increase in IFs in the patient group 2016–2017 might be the more frequent MRI and PET-CT scanning in this group compared to the patients treated in 2010–2011. Possibly, this might account for the larger amount of patients presenting with stage IV disease in the latter period.

A recent umbrella review of systematic reviews reported the pooled prevalence of incidentalomas in a combined population of cancer and non-cancer patients: 45% (95%CI: 36–55%) in chest CTs [16]. In the present study, a prevalence of 62% (2010–2011) and 72% (2016–2017) was found. An explanation for these increased numbers could be that our study population comprised of cancer patients only and the main risk factor for HNSCC is smoking [17]. Pulmonary nodules in smokers are fairly common [18]. In the umbrella study, unfortunately, no data on head and neck CT or MRI was analyzed.

In the limited literature describing incidental findings in HNSCC patients, the prevalence of IFs is much lower than in the present study, ranging between 35.2% (on PET-CT, [11]) and 37% [12]. These studies, however, differ in design compared to this study; the first focusing only on PET-CT IFs [11] and the second excluding IFs in head and neck region [12], which may explain the differences. In this study, PET-CT was the imaging modality showing the highest ratio of relevant IFs compared to all IFs found (65% of the total IFs were relevant IFs).

Our results demonstrated 10.1% of the relevant IFs to be malignant disease, similar to other reports (ranging between 3.5 and 19.4%) [11,12]. However in this report, patients with distant metastasis at

Table 2
Diagnostic evaluation and descriptive statistics of relevant incidental findings.

Characteristic	All (n = 592)	2010–2011 (n = 306)	2016–2017 (n = 286)	p-value
Diagnostic evaluation				**0.013**
No pathological lymph nodes	392 (66.2)	189 (61.8)	203 (71.0)	
Suspect pathological lymph nodes	195 (32.9)	116 (37.9)	79 (27.6)	
Pathological lymph nodes + distant metastasis(in retrospect)	5 (0.8)	1 (0.3)	4 (1.4)	
Incidental findings	364 (61.5)	152 (49.7)	212 (74.1)	**<0.001**
Relevant IF	128 (21.6)	43 (14.1)	85 (29.7)	**<0.001**
Anatomical location relevant IF:				0.257
Head and neck	15 (11.7)	6 (14.0)	9 (10.6)	
Thyroid	5 (3.9)	3 (7.0)	2 (2.4)	
Thorax	69 (53.9)	19 (44.2)	50 (58.8)	
Gastrointestinal	4 (3.1)	1 (2.3)	3 (3.5)	
Abdomen	14 (10.9)	8 (18.6)	6 (7.1)	
Genito-urinary	10 (7.8)	3 (7.0)	7 (8.2)	
Musculoskeletal or cutaneous	7 (5.5)	3 (7.0)	4 (4.7)	
Other	4 (3.1)	–	4 (4.7)	
Etiology relevant IF:				0.651
Miscellaneous	85 (66.4)	25 (58.1)	60 (70.6)	
Inflammatory	10 (7.8)	5 (11.6)	5 (5.9)	
Metabolic	2 (1.6)	1 (2.3)	1 (1.2)	
Vascular	6 (4.7)	2 (4.7)	4 (4.7)	
Benign tumor	12 (9.4)	4 (9.3)	8 (9.4)	
Synchronous primary tumor	9 (7.0)	5 (11.6)	4 (4.7)	
Metastasis	4 (3.1)	1 (2.3)	3 (3.5)	
Consequences relevant IF:				0.773
Radiologist recommendation	78 (60.9)	25 (58.1)	53 (62.4)	
Consultation or multidisciplinary meeting	10 (7.8)	3 (7.0)	7 (8.2)	
Intervention	8 (6.3)	2 (4.7)	6 (7.1)	
Multiple further actions	32 (25.0)	13 (30.2)	19 (22.4)	

IF: incidental finding. Etiology of relevant IF was retrospectively determined.

Table 3
Uni- and multivariable logistic regression analysis for CPI ≥ 30 days (n = 592).

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Patient characteristics				
Age (continuous)	0.98 (0.97–0.99)	**0.006**	0.99 (0.97–1.01)	0.445
Gender (female)	0.99 (0.70–1.41)	0.952		
ACE-27				
None	ref	ref		
Mild	1.06 (0.69–1.63)	0.776		
Moderate	0.95 (0.59–1.53)	0.841		
Severe	1.06 (0.56–1.99)	0.866		
Diagnostic evaluation				
Number of diagnostic investigations (continuous)	2.07 (1.80–2.39)	**<0.001**	/	
>2 diagnostic investigations	6.97 (4.81–10.10)	**<0.001**	/	
Presence of suspect lymph nodes	3.16 (2.24–4.45)	**<0.001**	1.23 (0.74–2.06)	0.420
Relevant IF present	2.40 (1.55–3.71)	**<0.001**	1.88 (1.08–3.28)	**0.026**
Consequences relevant IF:				
Radiologist recommendation	ref	ref		
Consultation or multidisciplinary meeting	1.20 (0.23–6.17)	0.827		
Intervention	0.50 (0.11–2.30)	0.373		
Multiple further actions	0.66 (0.26–1.65)	0.373		
Tumor and treatment				
Tumor site				
Oral cavity	ref	ref	ref	ref
Oropharynx	14.27 (7.46–27.30)	**<0.001**	2.13 (0.91–5.01)	0.083
Larynx	1.66 (1.13–2.44)	**0.010**	0.96 (0.56–1.65)	0.873
Hypopharynx	16.58 (4.95–55.55)	**<0.001**	2.97 (0.74–11.94)	0.125
Stage of disease				
Stage I	ref	ref	ref	ref
Stage II	5.11 (3.01–8.69)	**<0.001**	1.79 (0.89–3.60)	0.101
Stage III	6.61 (3.69–11.84)	**<0.001**	2.56 (1.21–5.42)	**0.014**
Stage IV	10.65 (6.77–16.75)	**<0.001**	4.36 (2.33–8.16)	**<0.001**
Treatment modality				
Surgery	ref	ref	ref	ref
Radiotherapy	25.26 (13.41–47.60)	**<0.001**	22.08 (10.62–45.90)	**<0.001**
Chemoradiation	21.77 (10.92–43.41)	**<0.001**	5.14 (2.12–12.48)	**<0.001**

ACE-27: Adult Comorbidity Evaluation, CI: confidence interval, IF: incidental findings, OR: odds ratio.
Diagnostic investigations and relevant IFs are not combined in the multivariable analysis due to collinearity in the statistical model.

diagnosis resulting in palliative treatment intention were excluded and are not taken into account in this percentage. In the management of IFs, no clear guidelines exists, although a report by Sahovaler et al. aims to provide tools for management of IFs [12].

This study points out that relevant IFs result in significant delay in treatment initiation. Relevant IFs could result in an unintended delayed oncological treatment since additional, originally unplanned diagnostic assessments are needed before deciding on the most appropriate treatment. Whether the IF was relevant and had to be taken into account in oncologic treatment decisions, only became clear after these additional efforts. Within our clinical experience, finding a (possibly relevant) IF during the diagnostic process might result in a temporary pause of the oncological pathway. We believe that the diagnostic investigations regarding the index HNSCC should be separated from other diagnostic investigations to avoid delay.

The effect of delay in treatment initiation is thought to be significant; tumor progression, resulting in more extensive treatment and worse overall survival [3–5]. Furthermore, IFs can create substantial psychological burden for patients as well as significant healthcare costs [19]. Therefore, a careful consideration in the interpretation of the incidental findings is important and prioritizing the next steps in the diagnostics and treatment is mandatory for each individual patient.

It should be noted that the median CPI has increased over the years, 27 days in 2010–2011 compared to 36 days in 2016–2017. This could be explained by the observed higher number of diagnostic investigations; more than twice as many patients received more than two diagnostic

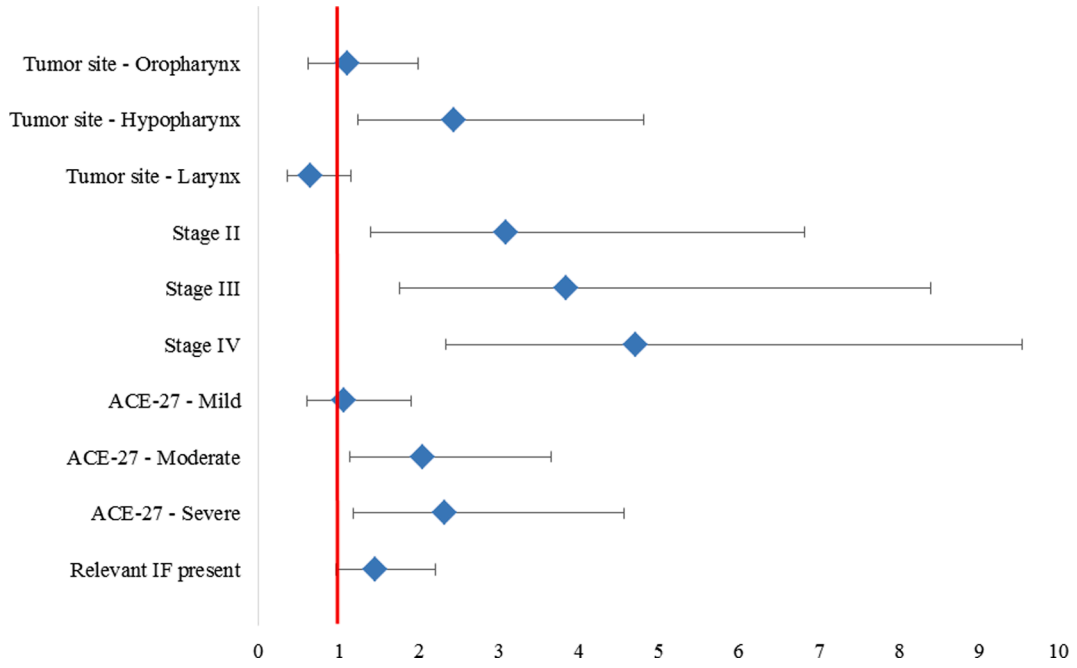

Fig. 3. Hazard Ratios of Dying in a multivariable model. ed vertical line indicating the reference set at 1.0. References categories are according to Supplementary Table 2. Exact Hazard Ratios, 95% confidence intervals and p-values are depicted in Supplementary Table 2 as well. ACE-27: Adult Comorbidity Evaluation, IF: Incidental Finding.

investigations.

These findings also raise questions about the additional value of the increasing number of diagnostic investigations performed over the years. For every diagnostic scan, also in diagnostic oncological work-up, the risks and benefits should be evaluated. Whereas certain risks of imaging tests, such as radiation exposure and nephrotoxicity for CT scanning with iodine-based contrast, are generally well-known [20,21], the risk of incidental findings (including their consequences and impact on timely treatment initiation) is often not anticipated by the clinician nor the patient.

Other independent determinants of CPI $\geq$ 30 days in our analysis were advanced stage tumors (stage III-IV) and treatment with (chemo) radiation. These findings are in line with recent reports [4,22–24] and may be explained by more extensive, multimodality therapy requiring considerable treatment planning for patients treated with radiotherapy.

Overall survival

A 1.46 times higher two-year overall mortality risk was found for patients with relevant IFs. An important side note is that this association was non-significant in the adjusted model. However, malignancy-related IFs seem to be contributing largely to this increased mortality risk (adjusted HR 2.54).

The effect of IF on survival can be interpreted in several ways. Relevant incidental findings may help in discovering potentially life-threatening disease (e.g. second primary malignancies, aneurysms) offering treatment in an early stage with better outcome; therefore, these findings may contribute to better survival chances. On the other hand, IFs may reflect potentially lethal diseases which can contribute to inferior life-expectancy. To fully understand the impact of IFs on survival, the disease-specific survival should be studied as well.

The identified independent factors associated with decreased overall survival, such as increasing age, moderate and severe comorbidities, hypopharyngeal tumors and stage II-IV tumors (compared to stage I) are in line with previously reported prognostic factors in HNC [2,25]. The increase in HPV positive oropharyngeal cancer may also be an explanation for the non-inferior survival of the latter period with increased CPI; however, data on HPV status was not available in this study.

Strengths and limitations

This study comprised a relatively large number of patients. All data was checked in detail and the presence of IFs was manually extracted from each electronic patient file and double-checked by two investigators. Another advantage of the present study is the very detailed data of the patients with multiple variables. Therefore, the database of the present study is large and reliable. Such laborious data is unlikely to be extracted from larger, national databases. However, a prospective study design would be preferable.

A complicating factor in this study is the strong correlation between the number of diagnostic investigations and the presence of a relevant IF. The more scans performed, the greater the chances of finding a relevant IF. Therefore, the distinction between the effect of diagnostic imaging on delay and presence of IF as cause of delay is almost impossible. Earlier reports of IFs did not study this relation nor mentioned the number of diagnostic investigations performed. Hence, it is difficult to put this findings in perspective.

Another choice that can be debated is whether to exclude patients without imaging as part of the diagnostic process (13.7%), since an IF as a result of imaging was not possible. However, since we were interested in the outcome variable delay in all patients entering the care pathway, and IF as a possible explanatory variable, we believe these patients should be included. However, this choice could be considered controversial; therefore, a sub-analysis only on the population with imaging was performed and presented as Supplementary Information (Supplementary Table 3 and 4). The results did not show a remarkable difference compared to the entire group, concerning the main message of the study.

Furthermore, for the survival analysis, adding disease specific survival (DSS) would provide more insight in the effect of IFs on survival. Unfortunately, DSS was not available in the database of the study.

Conclusion

In diagnostic work-up for HNSCC patients, relevant incidental findings are frequently encountered. As the frequency of additional imaging rises over the years, the number of IFs increased simultaneously. These relevant IFs yield clinical implications and this study is the first to describe the effect of relevant IFs on treatment delay: relevant IFs result in significant delay in treatment initiation.

Treating oncologists should be aware of this subsequent treatment delay. Clinical recommendations regarding management of relevant IFs are needed to provide guidance in prioritizing the next steps in treatment.

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Data availability statement

The data supporting the findings of this study are available on request through the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2021.105350.

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