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Insomnia, depression and anxiety in patients urgently referred with suspicion of head and neck cancer

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Main Article

Thomas Mullan takes responsibility for the integrity of the content of the paper

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Abstract

Objective. To determine differences in insomnia, depression and anxiety between ENT patients with benign and malignant conditions prior to and after an urgent suspicion of cancer appointment.

Methods. Out-patients with urgent suspicion of cancer completed three psychometric questionnaires prior to their appointment and at two to four weeks post-diagnosis.

Results. There was no significant difference in questionnaire scores between malignant and benign patients prior to the patients' appointments ($p > 0.05$ for all questionnaires). In benign patients, there was significant improvement in scores for all questionnaires ($p < 0.01$) and in malignant patients there was significant worsening of scores for all questionnaires ($p < 0.01$) at follow-up appointments.

Conclusion. Prior to appointments, patients with benign and malignant conditions experienced similar levels of insomnia, depression and anxiety. Following diagnosis, cancer patients had significantly poorer scores, indicating worsening of these symptoms. In patients with benign diagnoses, all questionnaire scores improved, indicating resolution of their symptoms and possible association between the appointment and their baseline scores.

Introduction

Patients presenting in Scotland's primary care with 'red flag' symptoms of head and neck cancer are referred urgently via the 'urgent suspicion of cancer' pathway. The aim of this pathway is to be seen by a specialist at the otolaryngology out-patient clinic within two weeks. The Scottish referral guidelines for suspected head and neck cancer detail these red flag symptoms.[1]

The 'urgent suspicion of cancer' and two-week referral pathways have been shown to be ineffective in identifying significant rates of head and neck cancer.[2,3] The proportion of patients attending the otolaryngology out-patient clinic with red flag symptoms of head and neck cancer who go on to receive a diagnosis of head and neck cancer has been shown to be as low as 3 per cent in Glasgow, with many patients being reassured and discharged after one visit with no forms of investigation.[4]

The prevalence of insomnia disorder in patients diagnosed with head and neck cancer is high before, during and after treatment.[5] It is well documented that those suffering from insomnia are at increased risk of depression and anxiety.[6,7] Both depression and anxiety have been demonstrated to be prevalent in head and neck cancer patients from the time of diagnosis well into the post-treatment period.[8]

It is unknown whether patients without cancer experience insomnia, depression or anxiety associated with 'urgent suspicion of cancer' referral for head and neck cancer. Given that a small proportion of these referrals result in a diagnosis of head and neck cancer, we investigated the psychological effects of an 'urgent suspicion of cancer' referral.

This study aimed to determine if there is any difference in median scores for three psychometric questionnaires (Insomnia Severity Index, Patient Health Questionnaire 9 and Generalised Anxiety Disorder Questionnaire 7) between benign and malignant patients prior to their referral appointments (baseline), and if there is any difference between these two groups at follow up. The study also aimed to assess the change from baseline to follow-up scores for both the benign and malignant groups.

Materials and methods

Data collection

Questionnaires were given to 227 eligible patients attending the otolaryngology out-patient clinic at the Queen Elizabeth University Hospital between October 2020 and March 2021. Patients who met the eligibility criteria were those aged 16 years or older attending with an 'urgent suspicion of cancer' referral. Information sheets were posted

to all eligible patients prior to clinic attendance. This allowed patients to decide whether or not to participate as well as to prepare questions before arrival.

Eligible patients completed the questionnaires prior to their clinic appointment. Patients were telephoned two to four weeks after their appointment to complete the questionnaires a second time; by this time, they would have been informed of their diagnosis. Patients were divided into a benign group and malignant group, depending on their diagnosis.

Insomnia Severity Index

The Insomnia Severity Index was used to assess the nature, severity and effect of insomnia.[9] The Insomnia Severity Index uses a five-point Likert scoring system (0 = no problem, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). Ranges in total score for the Insomnia Severity Index are 0–28, with a cut-off score of 10 having 86.1 per cent sensitivity and 87.7 per cent specificity for detecting insomnia cases.[9] A score of 0–7 indicates the absence of insomnia, 8–14 indicates subthreshold insomnia, 15–21 indicates moderate insomnia and 22–28 indicates severe insomnia. Evidence has shown the Insomnia Severity Index to be a reliable self-report measure to evaluate perceived sleep difficulties and a sensitive measure to detect changes in perceived sleep difficulties with treatment.[10]

Patient Health Questionnaire 9

The Patient Health Questionnaire 9 is used to diagnose depression. It is a nine-symptom checklist on which patients can self-report the severity of each symptom using a four-point Likert scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day).[11] This generates a score of 0–27, with a score greater than equal to 10 having sensitivity and specificity of 88 per cent for detecting major depressive disorder.[11] The Patient Health Questionnaire 9 score is interpreted as mild (scores of 5–9), moderate (scores of 10–14), moderately severe (scores of 15–19) or severe (scores of ≥ 20) depression.

Generalised Anxiety Disorder Questionnaire 7

This questionnaire screens for generalised anxiety disorder and assesses its severity. The Generalised Anxiety Disorder Questionnaire 7 is a seven-item checklist that scores the frequency of occurrence of the cardinal symptoms of generalised anxiety disorder on a four-point Likert scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day).[12] This generates a score of 0–21, with a cut-off score of 10 having 89 per cent sensitivity and 82 per cent specificity for a diagnosis of generalised anxiety disorder.[12] The Generalised Anxiety Disorder Questionnaire 7 score can be interpreted as mild (scores of 5–9), moderate (scores of 10–14) or severe (scores of ≥ 15) anxiety.

Statistical analysis

Kolmogorov–Smirnoff testing was used to assess the normality of total scores for each questionnaire at baseline and at follow up. This revealed that the spread of total scores was significantly different from a normal distribution ($p < 0.01$) for all questionnaires, both at baseline and at follow up. Thus, we decided to report median values. Mann–Whitney U testing was used to assess for differences in baseline median scores between the benign and malignant groups as well as any difference in the follow-up median scores between the benign and malignant groups. The Wilcoxon signed rank test was the paired test used to compare baseline and follow-up questionnaire scores for each diagnostic group (malignant or benign). Analysis was performed using SPSS software version 27.0.1.0.

Ethical considerations

The questionnaires were databased anonymously and research ethics committee approval was granted for the study. Informed, written consent was obtained from all participants.

Results and analysis

Patient demographics

Of the 227 patients who completed the questionnaires at their appointment, 208 (91.6 per cent) could be contacted via telephone call for the follow-up consultation. Of the 208 patients who were contacted, the mean age was 49.05 years; 126 (60.6 per cent) of the patients were female, 113 (54.3 per cent) were smokers or ex-smokers, 173 (83.2 per cent) recorded an alcohol intake within the weekly recommended rates, 151 (72.6 per cent) lived with their spouse, partner or family, 125 (60.1 per cent) had attained a higher education qualification, and 107 (51.4 per cent) were employed on a full or part-time basis.

Patients in the benign group were significantly younger and significantly less likely to be a smoker or ex-smoker. Patients in the benign group were more likely to be employed or in full-time education, and were less likely to live alone than patients in the malignant group (see Table 1 for all demographic information).

Diagnostic groups

Of the 208 patients included in the analysis, 185 (88.9 per cent) received a benign diagnosis and 23 (11.1 per cent) received a malignant diagnosis. Of the 23 malignancies, 17 (8.2 per cent) were diagnosed with primary head and neck cancer. The most common benign diagnosis was 'no abnormality detected', which was seen in 57 (30.8 per cent) of these patients. The most common malignant diagnoses were oral cancer, seen in 6 (26.1 per cent) of the patients, and laryngeal cancer, seen in 6 (26.1 per cent) of the patients. Oropharyngeal cancer, which is the most common form of head and neck cancer globally, was seen in 5 (21.7 per cent) of the patients with malignancies. The varieties of benign and malignant diagnoses are reported in Tables 2 and 3.

Insomnia Severity Index

For the Insomnia Severity Index, there was no significant difference in baseline median scores between the benign and malignant groups ($p = 0.914$), with both median scores corresponding to 'subthreshold insomnia'. At follow up, there was a statistically significant difference in the median scores between the benign and malignant groups ($p < 0.01$), with the median score in the benign group corresponding to an 'absence of insomnia' and the median score in the malignant group corresponding to 'moderately severe insomnia'.

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Table 1. Demographic information for all patients and main diagnostic groups

Demographic variable	All patients*	Benign group†	Malignant group‡	*p*-value
Sex (*n* (%))				
– Male	82 (39.4)	72 (38.9)	10 (43.4)	>0.05
– Female	126 (60.6)	113 (61.1)	13 (56.6)	>0.05
Age (mean (range) years)	49.05 (16–87)	47.84	58.78	<0.05
Smoking status (*n* (%))				
– Current smoker or ex-smoker	113 (54.3)	96 (51.9)	17 (73.9)	<0.05
– Never smoked	95 (45.7)	89 (48.1)	6 (26.1)	<0.05
Alcohol intake status (*n* (%))				
– Within recommended UK limit	173 (83.2)	155 (83.8)	18 (78.3)	>0.05
– More than recommended UK limit	35 (16.8)	30 (16.2)	5 (21.7)	>0.05
Housing (*n* (%))				
– Married, or living with partner or family	151 (72.6)	136 (73.5)	15 (65.2)	>0.05
– Lives alone	49 (23.6)	42 (22.7)	7 (30.4)	>0.05
– Residential care	8 (3.8)	7 (3.8)	1 (4.3)	>0.05
Employment (*n* (%))				
– Full- or part-time employment	107 (51.4)	98 (53.0)	9 (39.1)	<0.05
– Full-time education	15 (7.2)	15 (8.1)	0	<0.05
– Not employed or retired	86 (41.4)	72 (38.9)	14 (60.9)	<0.05
Education (*n* (%))				
– College or university qualification	125 (60.1)	112 (60.5)	13 (56.5)	>0.05
– No higher education	83 (39.9)	73 (39.5)	10 (43.5)	>0.05

*$n = 208$; †$n = 185$; ‡$n = 23$

There was a significant reduction in the Insomnia Severity Index score from baseline to follow up in the benign group ($p < 0.01$), indicating improved sleep. There was a significant increase in Insomnia Severity Index score from baseline to follow up in the malignant group ($p < 0.01$), indicating worsening sleep. Scores for the Insomnia Severity Index are shown in Figure 1.

Patient Health Questionnaire 9

For Patient Health Questionnaire 9, there was no statistically significant difference in the baseline median scores between the benign and malignant groups ($p = 0.254$), with median scores for both groups corresponding to 'mild depression'. At follow up, there was a statistically significant difference in the median scores between the benign and malignant groups ($p < 0.01$), with the median score for the benign group corresponding to 'no depression' and the median score for the malignant group corresponding to 'moderately severe depression'.

There was a significant reduction in median Patient Health Questionnaire 9 scores from baseline to follow up in the benign group ($p < 0.01$) indicating less severe symptoms of depression. There was a significant increase in the median score from baseline to follow up in the malignant group ($p < 0.01$), indicating more severe symptoms of depression. Scores for Patient Health Questionnaire 9 are shown in Figure 2.

Generalised Anxiety Disorder Questionnaire 7

For Generalised Anxiety Disorder Questionnaire 7, there was no significant difference in baseline median scores between the benign and malignant groups ($p = 0.330$), with median

Table 2. Benign diagnoses

Benign diagnosis	Participants* (*n* (%))
No abnormality detected	57 (30.8)
Globus	11 (5.9)
Benign larynx	12 (6.5)
Reactive lymph nodes	34 (18.4)
Benign thyroid	21 (11.4)
Benign salivary	12 (6.5)
Benign oropharynx	7 (3.8)
Benign neck	25 (13.5)
Benign oesophagus	6 (3.2)

*$n = 185$

Table 3. Malignant diagnoses

Malignant diagnosis	Participants* (*n* (%))
Malignant oropharynx	5 (21.7)
Malignant oral	6 (26.1)
Malignant larynx	6 (26.1)
Malignant thyroid	2 (8.7)
Lymphoma	2 (8.7)
Metastases	2 (8.7)

*$n = 23$

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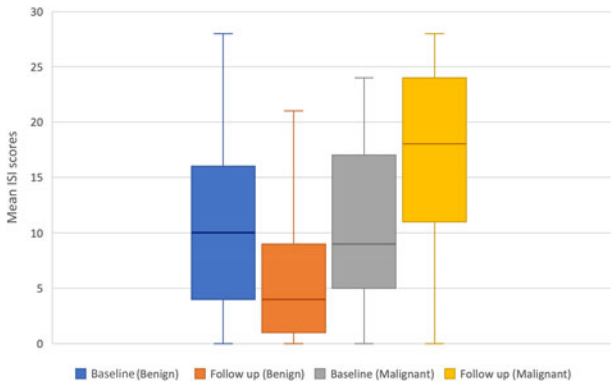

Figure 1. Boxplot illustrating scores for the Insomnia Severity Index (ISI). The horizontal line inside each box shows the median. Whiskers indicate variability outside upper and lower quartiles.

scores for both groups corresponding to 'no anxiety'. At follow up, there was a statistically significant difference in scores between the benign and malignant groups ($p < 0.01$), with the median score for the benign group corresponding to 'no anxiety' and the median score for the benign group corresponding to 'severe anxiety'.

Generalised Anxiety Disorder Questionnaire 7 scores show a significant decrease from baseline to follow up in the benign group ($p < 0.01$), indicating improvement in anxiety symptoms. Median scores in the malignant group showed a significant increase from baseline to follow up ($p < 0.01$), indicating worsening anxiety symptoms. Generalised Anxiety Disorder Questionnaire 7 scores are shown in Figure 3.

We also recorded mean scores for each questionnaire at baseline and follow up, which are included in Tables 4 and 5.

Discussion

Comparison of benign and malignant groups

We showed that symptoms of insomnia, depression and anxiety in the malignant group were similar to those of the benign group prior to the appointment. At follow up, we showed that symptoms were significantly worse in the malignant group compared to the benign group. With regard to patient demographics, analysis showed that patients diagnosed with cancer

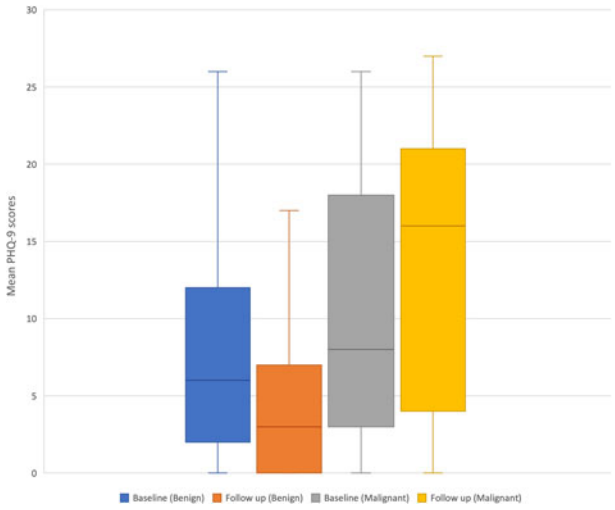

Figure 2. Boxplot illustrating scores for the Patient Health Questionnaire 9 (PHQ-9). The horizontal line inside each box shows the median. Whiskers indicate variability outside upper and lower quartiles.

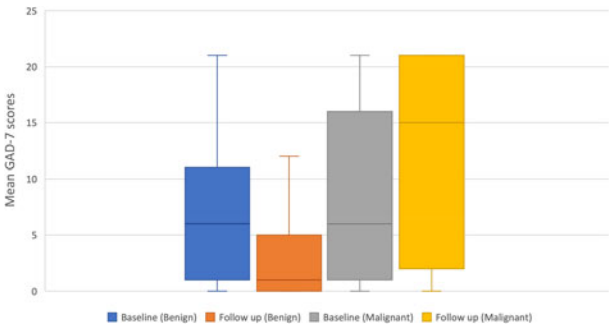

Figure 3. Boxplot illustrating scores for the Generalised Anxiety Disorder Questionnaire 7 (GAD-7). The horizontal line inside each box shows the median. Whiskers indicate variability outside upper and lower quartiles.

at the clinic were significantly older, and more likely to be smokers or ex-smokers, which are important risk factors for the development of head and neck cancer.[13]

Benign group (baseline versus follow up)

The significant improvement in the median scores in the benign group for all questionnaires suggests that there is likely a degree of sleep disturbance, depression and anxiety prior to the appointment, which improves following a benign diagnosis. Whilst these symptoms appear to be mild, it is important to recognise that benign referrals make up the majority of these 'urgent suspicion of cancer' referrals.

Malignant group (baseline versus follow up)

The significant deterioration in median scores in the malignant group for all questionnaires is unsurprising; a diagnosis of cancer is associated with significant psychological distress, and existing literature shows the prevalence of insomnia, depression and anxiety to be high in head and neck cancer patients following their diagnosis.[14]

Head and neck cancer rate

The cancer rate for patients in our sample was 11.1 per cent, with 8.2 per cent of these being primary head and neck cancers. This is similar to the findings of a large 2016 systematic review and meta-analysis, which reported a pooled two-week referral conversion rate for head and neck cancer rate of 8.8 per cent (95 per cent; confidence interval = 7–10.7 per cent).[15] However, a 2020 study showed a detection rate for head and neck cancer as low as 3 per cent in patients attending urgent referral appointments in Glasgow.[4] The reason for this increased detection rate in our sample is unclear. However, one possible explanation may be the effects of coronavirus disease 2019, with most patients attending hospital appointments only if strictly necessary and with more severe symptoms.

Importance of study

Critics of the two-week referral process have claimed that only a small proportion of people referred this way are diagnosed with cancer, that the referral has little effect on survival and that referring patients in this manner is expensive. Those in support of the process claim it ensures consistency in the management of cancer patients and that patients value the process. Literature on the psychological effects of a two-week urgent referral is limited, and relates to other forms of malignancy such as breast and colorectal carcinoma.[16,17] Cornfold *et al.*

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Table 4. Mean scores for all questionnaires at baseline and follow up in benign group

	Insomnia Severity Index		Sleep Condition Indicator		Patient Health Questionnaire 9		Generalised Anxiety Disorder Questionnaire 7	
Parameter	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Mean	10.75	6.40	17.69	21.82	7.75	4.92	6.73	3.66
SD	7.076	6.906	8.575	8.750	6.870	6.421	5.875	5.383

SD = standard deviation

Table 5. Mean scores for all questionnaires at baseline and follow up in malignant group

	Insomnia Severity Index		Sleep Condition Indicator		Patient Health Questionnaire 9		Generalised Anxiety Disorder Questionnaire 7	
Parameter	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Mean	10.78	16.87	16.35	14.17	10.09	13.30	8.52	12.61
SD	7.822	8.651	9.053	10.030	8.399	9.276	7.627	8.856

SD = standard deviation

conducted a qualitative study and found that women referred via a two-week urgent referral experienced considerable anxiety from the time of their referral to diagnosis.[16] They also identified that patients felt the need for more information about breast cancer symptoms and the referral process itself.[16] Ndukwe *et al.* also conducted a qualitative study interviewing patients who had been referred under the two-week rule for suspected colorectal cancer.[17] They concluded that patients appreciated the speed of the referral process and welcomed further investigations, but that the process caused them significant levels of anxiety and distress. They identified that two areas in which the psychological effects of the referral could be reduced would be by providing early psychological support as well giving patients more information about the investigative process.[17]

- Cancer detection rates from urgent head and neck cancer referrals remains low
- Head and neck cancer patients are at increased risk of insomnia, depression and anxiety, from time of diagnosis and throughout the treatment pathway
- No study has investigated the effects of an urgent suspicion of cancer referral on patients who ultimately received a benign diagnosis
- Patients with malignancy diagnoses show worsening levels of insomnia, depression and anxiety
- Following a benign diagnosis, insomnia, anxiety and depression symptoms resolve, indicating these symptoms were partly related to clinic attendance
- Improvements to urgent head and neck cancer referrals could reduce insomnia, depression and anxiety in benign patients

Cancer detection rates from these urgent referrals have been shown to be particularly low in several recent studies, suggesting that the pathway is being significantly overused.[4,18,19] Future measures to improve how we filter out the vast majority of benign patients might avoid these symptoms and improve the patient journey.

Study strengths

The study strengths include a large sample of benign patients and the use of questionnaires that have been extensively validated. These questionnaires also have been shown to be sensitive to change, which was crucial for this study. The follow-up rate in our study was also very good, with 208 (91.6 per cent) of the originally consented patients completing the follow-up questionnaires.

Study limitations

The small size of the malignant group reduced the reliability of these findings. There was no other qualitative information on the patients' sleep or mental health recorded at follow up, which may have been helpful in establishing the exact reasons for changes in score. Previous diagnoses of insomnia, depression and anxiety were not recorded, which would have been useful because patients would be likely to report severe symptoms regardless of whether the appointment had been concerning them or not. Whilst these questionnaires have undergone extensive validation, little data exists on what a mean or median score for the general population would be, which would have provided a useful comparison.

Clinical implications

This study's findings add weight to the proposition that the approach to urgent head and neck cancer referrals should be improved. Such improvement may be achieved through use of a head and neck risk calculator in the primary care setting. A head and neck risk calculator has been shown to have significant potential to improve health service delivery by reducing the number of inappropriately urgent referrals.[20] Reduction in the number of inappropriate referrals could avoid the adverse effects of insomnia, depression and anxiety in the patients who would ultimately receive a benign diagnosis.

The management of head and neck cancer patients (and cancer patients generally) could be improved by screening newly diagnosed patients for insomnia, depression and anxiety. Early detection of these symptoms would allow them to be referred to the appropriate services and/or receive appropriate treatment to help manage these symptoms as the patients enter cancer treatment.

Conclusion

Prior to a referral for suspicion of head and neck cancer, patients with both benign and malignant conditions

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experienced similar levels of insomnia, depression and anxiety. Insomnia, depression and anxiety worsened in the patients who received a malignant diagnosis. In the patients who received a benign diagnosis, scores for all questionnaires significantly improved. Improvement of these scores at follow up indicates that feelings of insomnia, depression and anxiety were, in part, related to the clinic attendance.

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Competing interests. None declared

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