


SYSTEMATIC REVIEW

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Treatment priorities and regret in older adults with head and neck cancer: A systematic review

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Abstract

Background: The majority of head and neck cancer (HNC) diagnoses are seen in people aged 70 and older; these numbers are set to increase. Greater understanding of treatment needs of older patients with HNC is essential. These older patients often have co-existing health conditions, are prone to frailty and may not prioritise survival when considering treatment options. This systematic review examines the current research with regard to priorities and factors influencing treatment regret in older people with HNC.

Methods: Studies were eligible for inclusion if they (i) reported data from patients with a mean age of 65 years or older who had a confirmed diagnosis of HNC and had been treated using surgery, chemotherapy and/or radiotherapy with either palliative or curative intent, (ii) considered patient's priorities or preferences or examined treatment regret as one of the primary outcomes of the study (iii) were published in English.

Results: Pilot search identified $n = 7222$ articles; however, following screening, only four papers met the inclusion criteria. Narrative synthesis was indicated to analyse quantitative and qualitative evidence in parallel, as meta-analyses were not possible.

Discussion: There is a paucity in the literature examining older adults with HNC. There is an indication that older adults prioritise maintaining independence when making treatment decisions and treatment regret is seen in those with high levels of depression with level of frailty also a contributing factor. Clinicians should consider patient's social circumstances, premorbid status and priorities in maintaining independence and managing symptoms when making treatment decisions in this cohort.

KEYWORDS

frailty, head and neck cancer, older, priorities, treatment regret

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1 | INTRODUCTION

Older adults are significantly under-represented in the head and neck cancer (HNC) literature and are frequently excluded from clinical trials; as a result decision-making in this cohort is difficult. Globally, the population of adults >65 is growing faster than any other age group¹ with the World Health Organization defining 'older people' as those aged 60 or older.² In the United Kingdom, over 12 000 new cases of HNC are diagnosed annually, with the highest incidence in those over 70 years of age³; with an ageing population, these numbers are set to increase. As this population profile changes, greater understanding of treatment decision-making for older people with HNC is essential.

Treatment with curative intent can be aggressive and protracted involving a combination of surgery, radiotherapy or chemotherapy. Patients treated palliatively usually die within 1 year of diagnosis.⁴ Both the disease and its treatment can lead to substantial, multiple chronic physical and psychosocial conditions. Most common are difficulties with swallowing and malnutrition, which in turn increase the risk of developing frailty.⁵ These symptoms can persist long term and significantly impact the quality of life.⁶ Current guidance for HNC treatment neglects the many issues commonly affecting older adults, such as multiple chronic conditions, frailty, maintaining independence and difficulties with activities of daily living. These factors may directly impact people's priorities with regard to treatment options and decision-making.

Research into treatment priorities has focused on younger HNC patients with curing cancer and prolonging life rated as their top concerns.⁷ Preliminary research suggests that older adults' priorities differ with maintaining independent living and pain management being at the fore.⁷⁻⁹ Treatment regret may be experienced when it is suspected that an alternative course of action would have resulted in a better outcome, that is, where patient's priorities are not addressed and functional outcome and visual appearance differ from expectation.¹⁰

We must develop a better understanding of the unique considerations appropriate for the older patient when discussing treatment objectives and treatment burden. The purpose of this review is to identify the priorities of older people with HNC and factors that influence treatment regret to support information and shared decision-making in this patient cohort.

2 | METHODOLOGY

2.1 | Review conduct and reporting

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidance.¹¹ The protocol was registered on Prospero, an international prospective register of systematic reviews, hosted by the University of York (reg. number CRD42022321799) and can be accessed at <https://www.crd.york.ac.uk/PROSPERO>.

Key Points

1. The majority of head and neck cancer (HNC) diagnoses are in people aged 70 years or older and set to increase.
2. There is a paucity in research examining older adults with HNC.
3. There is an indication that older adults prioritise maintaining independence when making treatment decisions.
4. Treatment regret is seen in those with high levels of depression with level of frailty also a contributing factor.
5. Clinicians should consider patient's social circumstances, premorbid status and priorities when making treatment decisions.

2.2 | Search strategy

A search strategy was developed in collaboration with the research team and a systematic review specialist. Search terms were formulated to identify articles specifically relating to priorities and treatment regret for older patients with HNC. The full search strategy terms are detailed in Appendix 1.

Six electronic databases, Medline (including PubMed), EMBASE, CINAHL, EMCARE, PSYCHINFO and Cochrane Library, were systematically searched for published literature. Both Medical Subject Heading terms and text word searches were used to increase sensitivity in addition to Boolean operators 'OR' and 'AND' to expand or limit search results. This was completed in consultation with an experienced subject librarian. For review of full search strategy, see Appendix 2.

2.3 | Eligibility criteria

Studies were eligible for inclusion if they (i) reported data from patients with a mean age of 65 years or older who had a confirmed diagnosis of HNC and had been treated using surgery, chemotherapy and/or radiotherapy with either palliative or curative intent (HNC was defined as any cancer of the head or neck apart from thyroid cancer. Thyroid cancer was excluded because of its unique histology and treatment parameters) (ii) considered patient's priorities or preferences or treatment regret or dissatisfaction as one of the primary outcomes of the study, validated measures were not a requirement for inclusion (iii) were published in English.

Commentaries, conference abstracts, dissertations, editorials and review articles were excluded. There was no time limit on publication and no restrictions on study design or size to ensure inclusivity of all data sources.

2.4 | Screening and selection

All papers identified from the search strategy were downloaded to a reference software (Mendelay) and were screened by the primary reviewer

(Emer Fahy) for duplicates. Two reviewers independently screened the titles (Emer Fahy and Ahmed El Batal). Abstracts were then transferred to Rayyan, enabling systematic documentation for inclusion/exclusion. The abstracts were screened by two reviewers (Emer Fahy and Linda A. Cantwell) with any discrepancies or uncertainties discussed with a third reviewer (Joanne M. Patterson). The full-text papers of potentially eligible studies were then reviewed against the eligibility criteria. Discrepancies were discussed with the wider research team (Emer Fahy, Linda A. Cantwell, Joanne M. Patterson and Simon Rogers) until a negotiated conclusion was reached.

2.5 | Data extraction

A data extraction form was designed for use for the review. For each study, relevant demographic, methodological and summary data were extracted and independently checked for accuracy. The following

information was extracted: (i) author, (ii) year of publication, (iii) study design, (iv) clinical and treatment characteristics of the participants (tumour location, stage and treatment type), (v) measurements used for the examined outcome and the time points these measurements were taken (vi) main findings and (vii) frailty measurements. Data were analysed narratively; heterogeneity in study findings precluded meta-analysis.

The primary outcome was to examine the priorities of older adults with HNC and what factors influence treatment regret.

A secondary outcome was to examine the inclusion of frailty as a descriptor or measurement in understanding patient priorities and whether it is influential in treatment regret.

2.6 | Quality assessment

The Newcastle Ottawa Quality Assessment scale¹² was selected as a quality measurement for cohort studies. Quality assessment was

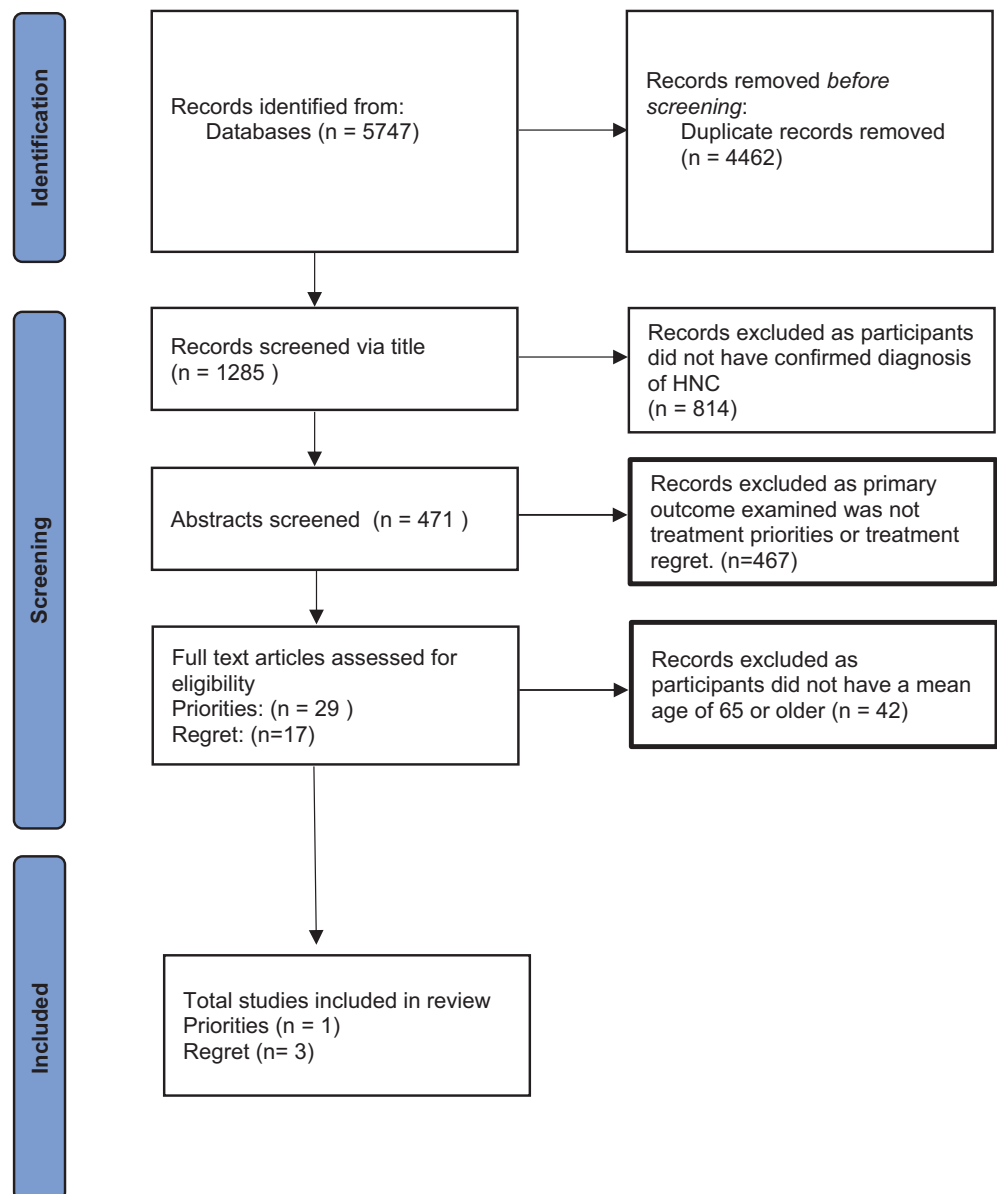


FIGURE 1 PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

TABLE 1 Study characteristics.

Study lead author	Year	Study location	Study design	Study aim	Sample size	Patient characteristics—Male (%)	Patient characteristics mean age (SD)	Outcome examined
Thomas	2019	Canada	Prospective Cohort Study	To assess whether age and frailty are associated with preoperative depression and postoperative decision regret in patients undergoing major head and neck surgery and to identify additional factors associated with depression and decision regret.	274	206 (75%)	67.8 (9.5)	Treatment Regret
Van Essen	2022	The Netherlands	Prospective Cohort study	To study the health outcome priorities of older patients with HNC, and to evaluate whether general health, markers of physical, cognitive and social functioning and quality of life are associated with health outcome prioritisation.	170	122 (72%)	77.8 (5.5)	Treatment Priorities
Macias	2021	USA	Cross-Sectional Study	To assess the association of demographic and oncological characteristics with HNC-related body image distress.	301	212 (70%)	65.3 (11.7)	Treatment Regret
Melissant	2022	The Netherlands	Mixed Methods Cross-sectional Study	To investigate the prevalence of body image distress among HNC patients after treatment and to examine its association with sociodemographic and clinical factors.	233	154 (66%)	67 (10.7)	Treatment Regret

conducted by the primary reviewer, with second reviewer (Linda A. Cantwell) for consensus.

3 | RESULTS

3.1 | PRISMA diagram

There were four papers in total which met the inclusion criteria (Figure 1).

3.2 | Study details, patient cohort and treatment

All four papers were cohort studies from the United States, Canada and the Netherlands, with 170–300 participants per study (Table 1).

All participants had a mean age > 65 with a diagnosis of confirmed HNC. All treatment intents were represented; surgical ± oncological. Two studies did not define their treatment intent, one with curative intent only and the other including all treatment intent. The studies were completed at varying time points pre- and post-treatment (Table 2).

3.3 | Frailty measurement

Two studies used a measurement of frailty.^{13,14} One included a comprehensive geriatric examination involving a thorough interview, physical examination, EEG and Mini-Mental State Examination, examination of activities of daily living, nutritional assessment and review of risk of pressure sores. The other was less detailed simply collecting the Adult Comorbidity Evaluation–27 and Fried Frailty Index (Table 3).

TABLE 2 Treatment characteristics.

Paper author (year)	Tumour site no. (% cohort)	Treatment received	Treatment intent	Length of time post-treatment study completed
Thomas (2019)	Mucosal (oral cavity, oropharynx, larynx and hypopharynx): 157 (58.3%) Non-mucosal (cutaneous, thyroid and salivary gland): 113 (41.7%)	Planned for surgery	Not defined	Measurements taken preoperatively, 3-month post-surgery, 6-month post-surgery and 12-month post-surgery
Van Essen (2022)	Skin: 25 (14.7%) Oral cavity: 35 (20.6%) Vestibulum nasi: 7 (4.1%) Sino nasal: 13 (7.6%) Salivary glands 8 (4.7%) Oropharynx: 17 (10%) Nasopharynx: 1 (0.6%) Hypopharynx: 20 (11.8%) Larynx: 39 (22.9%) Unknown primary: 5 (2.9%)	Not defined	Curative (83.5) and palliative intent (16.5%)	Measures taken pre-treatment
Macias (2021)	Oral cavity: 129 (42.9%) Oropharynx: 50 (16.6%) Larynx/hypopharynx: 38 (12.6%) Unknown/other: 14 (4.7%) Major salivary gland: 20 (6.6%) Facial cutaneous malignancy: 50 (16.6%)	Surgery: 115 (38.2%) Surgery and adjuvant radiation: 98 (32.6%) Surgery and adjuvant chemoradiation: 88 (29.2%)	Not defined	0–6 months: 119 (39.5) 6–12 months: 49 (16.3) 12–24 months: 52 (17.3) >24 months: 81 (26.9)
Melissant (2022)	Oral cavity: 51 (22%) Oropharynx: 57 (25%) Hypopharynx: 12 (5%) Larynx: 64 (28%)	Single treatment: 111 (48%) Surgery: 62 (56%) Among which CO ₂ laser: 33 (53%) Radiotherapy: 49 (44%) Combination treatment: 122 (52%) Chemoradiotherapy: 51 (42%) Surgery and (chemo) radiotherapy: 70 (57%) Other: 1 (0.8%)	Curative intent	Between 6-week and 5-year post-treatment

TABLE 3 Priorities results.

Study and outcome examined	Outcome measurement	Results	Frailty measurement	Newcastle Ottawa Scale Quality assessment
Van Essen et al. ¹⁴ Priorities	Outcome Prioritisation Tool (OPT) ¹⁵ European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) ¹⁶	OPT First Priority: 53% maintaining independence 34.1% life extension 8.2% reducing pain 4.1% reducing other symptoms OPT Second Priority: 34.1% Staying alive and maintaining independence 19.5% reducing pain 12.2% reducing other symptoms Influences: Housing situation related significantly to first priority ($p = .029$) Living alone prioritised reducing pain or other symptoms Living with family increasingly prioritised life extension and maintaining independence MSK issues prioritised reducing pain and other symptoms.	Comprehensive Geriatric Assessment: (i) A thorough interview containing patient's medical and psychiatric history, use of medication, sociodemographic status and general complaints; (ii) physical examination (general, psychiatric, neurological); (iii) additional measurements such as laboratory measurements, electrocardiogram, and the Mini-Mental State Examination (MMSE); and (iv) completion of various forms examining activities of daily living, the OPT, nutrition and pressure sores screening tools	Poor Quality (3/9 stars)
Thomas et al. ¹³ Treatment Regret	Vulnerable Elders Survey (VES-13) ¹⁷ Bradburn Scale of Psychological Well-Being (BSPW-B) ¹⁸ IADL ¹⁹ European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) ¹⁶ Geriatric Depression Scale (GDS) ²⁰ Decision Regret Scale (DRS) ²¹	Mean DRS score 18.2 indicating overall mild decision regret. Univariable baseline factors associated with moderate to severe decision regret 6 months after surgery included a higher Fried Frailty Index score (OR, 1.38 [95% CI, 1.01–1.90]), higher depression scores (OR, 1.17 [95% CI, 1.06–1.28]), lower Lawton-Brody IADL Questionnaire scores (i.e., increased dependence) (OR, 0.85 [95% CI, 0.75–0.97]) and lower score on the BSPW-B (OR, 0.78 [95% CI, 0.68–0.91]). Both the preoperative and 6-month postoperative EORTC QLQ-C30 summary score was associated with moderate to severe decision regret at 6 months. In MVA models, only a higher preoperative depression score was associated with moderate to severe decision regret (OR, 1.17 [95% CI, 1.06–1.28]).	Adult Comorbidity Evaluation-27 (ACE27) Fried Frailty Index (FFI)	Average Quality (4/9 stars)
Macias et al. ²² Treatment Regret	IMAGE-HN (Inventory to Measure and Assess imaGe disturbance-Head & Neck)	Higher educational attainment was associated with lower social avoidance and isolation subdomain scores. Graduation from college ($\beta = -9.6$; 95%	Not measured	Poor Quality (1/9 stars)

TABLE 3 (Continued)

Study and outcome examined	Outcome measurement	Results	Frailty measurement	Newcastle Ottawa Scale Quality assessment
	Self-reported sociodemographic and oncological questionnaire ²³	CI, -17.5 to -1.7) or graduate school ($\beta = -12.6$; 95% CI, -21.2 to -3.8) was associated with 9.6-point and 12.6-point lower IMAGE-HN social avoidance and isolation subdomain scores compared with non-high school graduates. Disability was associated with an increased IMAGE-HN global ($\beta = 5.1$; 95% CI, 0.1-10.0) score compared with part-time or full-time paid work. Unemployment had a positive association with IMAGE-HN global ($\beta = 8.0$; 95% CI, 0.6-15.4) scores as well as other-oriented appearance concerns ($\beta = 10.7$; 95% CI, 2.0-19.3) and personal dissatisfaction with appearance ($\beta = 12.5$; 95% CI, 1.2-23.7) subdomain scores when compared with paid employment.		
Melissant et al. ²⁴ Treatment Regret	Body Image Scale (BIS) ²⁵ EORTC QLQ-C30 ²⁶ EORTC QLQ-HN43 ¹⁶ Female Sexual Function Index (FSFI) 6 item for women ²⁷ International Index of Erectile Function (IIEF-5) 5 item for men ²⁸ Self-Compassion Scale-Short Form (SCS-SF) ²⁹ Hospital Anxiety and Depression Scale (HADS) and subscale for anxiety and depression (HADS-A, HADS-D) ³⁰	The prevalence of body image distress was 13% (cut-off ≥ 10) to 20% (cut-off ≥ 8) (median = 2, IQR = 0-6). Univariate logistic regression analyses showed that age, gender, education level, treatment modality, surgery extent, EORTC QLQ-C30 summary score, all QLQ-HN43 subscales, self-compassion and psychological distress were significantly associated with body image distress. The multiple logistic regression model showed that five factors were significantly and independently associated with body image distress: symptoms of depression, younger age, problems with social contact, problems with wound healing and larger extent of surgery.	Not measured	Average Quality (4/9 stars)

Abbreviations: CI, confidence interval; IQR, interquartile range; MSK, musculoskeletal; MVA model, multivariate analysis; OR, odds ratio.

3.4 | Quality assessment

The methodological quality of the studies was assessed using the Newcastle-Ottawa scale,¹² which allocates a maximum of nine stars each to case selection, comparability of cohorts and outcomes assessment. A study awarded six or more stars were considered as a high-quality study.

There were two studies of poor methodological quality^{14,22} and two of average quality.^{13,24} Full breakdown of star allocation is in Appendix 2. The key strengths were that three of four studies had cohorts that were relatively or truly representative of the average patient group and three of four used secure health records for exposure data. The predominant issues in quality for our studies lay in the

quality of the outcomes; this included lack of varying outcome measurements and time points measurements.

3.5 | Outcomes

3.5.1 | Priorities

The results illustrated that people prioritised maintaining their independence most highly as their top priority (53%), followed by life extension (34.1%), reducing pain (8.2%) and reducing symptoms (4.1%). A similar pattern was seen for second priority with the majority of people (34.1%) choosing to stay alive and maintain independence, followed by reducing pain (19.5%) and reducing other symptoms (12.2%).

The priorities chosen were influenced by a person's living circumstances. Those living alone prioritised reducing pain or other symptoms, whereas those living with family were more likely to prioritise life extension and maintaining independence.

3.5.2 | Treatment regret

Thomas et al.¹³ showed an overall mean Decision Regret Score (DRS) score of 18.2, indicating overall mild decision regret. Baseline factors associated with moderate–severe decision regret included a higher Fried Frailty Index, higher depression scores, lower Lawton Brody Instrumental Activities of Daily Living score (indicative of increased dependence) and lower Bradburn scale (indicative of less happiness), although in MVA analysis only high preoperative depression scores were associated with DRS.

Macias et al.²² and Mellissant et al.²⁴ focused on the factors associated with body image distress (BID). One study detailed the prevalence of 13%–20% BID in its participants,²⁴ whereas the other presented nil details of prevalence of BID.²² Macias et al.²² found that higher educational attainment was associated with lower social avoidance and isolation subdomain scores. Disability was also associated with an increase in IMAGE-HN global score compared with part-time or full-time work. Unemployment had a positive association with other orientated appearance concerns, and personal dissatisfaction with appearance compared to paid employment.

Melissant et al.²⁴ also found that symptoms of depression were associated with BID. In addition to depression, they saw that younger age, problems with social contact, that is, social isolation, problems with wound healing following surgery and larger extent of surgery were associated with BID.

4 | DISCUSSION

The intention of this review was to identify the priorities of older people in addition to identifying factors that influence treatment regret. There is a paucity of research in this area with just a small number of studies meeting the inclusion criteria with large variability in the study

characteristics. However, the available evidence indicates that older adults with HNC may have a higher preference for maintaining their independence when making decisions about their treatment and decision regret is impacted by high levels of depression with frailty also a contributing factor.

Acknowledging their limitations given the small number of included papers, our findings are generally in line with the literature focusing on the priorities of people with HNC, which show that older adults have a unique set of priorities compared to younger adults. Bonomo et al.⁷ noted only 84% and 43% of subjects older than 65 years placed 'being cured of my cancer' and 'living as long as possible' in their top three rankings compared with 98% and 73% of those younger than 55 years, respectively. Other similar studies demonstrate that older patients are less likely to rank 'cure' or longevity⁹ higher than 'having no pain' in their top three priorities compared to younger patients.^{8,10} Pain is reported in approximately one third of people with HNC and can be a symptom of the disease as well as a treatment side effect.³¹ These studies indicate the need for careful consideration of treatment decisions for older people, given the myriad of side effects these treatments bring in conjunction with people's priorities and expectations for treatment.

This review identified that a patient's living circumstance substantially influenced priorities with those co-habiting being more likely to prioritise life extension and maintaining independence.¹⁴ This is a little examined factor in the treatment of older adults—the effects of treatment choices on independence and activities of daily living in addition to the carer burden that is borne by their families. There is a significant increase in dependency observed in people aged ≥ 70 years old, compared with pre-treatment status with a greater need for assistance with activities of daily living.^{32,33} Carer burden is high for those supporting people with HNC.³⁴ For older adults, a loss in independence will increase the need for care, placing additional burden on family and healthcare services.

Treatment decision regret provides an insight into reasons for perceived 'wrong treatment decision' and may indicate where treatment priorities are not met. Although three papers met our inclusion criteria, none of these focused solely on an older population, although their mean population happened to be >65 . Mild decision regret appears relatively common (up to 46%) across all age groups of HNC patients.^{35,36} Factors which influence decision regret are less widely reported; it was seen in the older group that depression increased decision regret. Regret can also manifest itself in body image dissatisfaction following treatment, as seen in a study by Gibson et al.,³⁷ where some patients demonstrated regret secondary to the level of disfigurement seen following treatment. Our review identifies that psychological distress and depression influence both body image dissatisfaction and treatment regret further evidencing the need to review all facets of patient's lives to facilitate holistic decision-making.

4.1 | Treatment decision-making

Optimal treatment pathways for older adults with HNC are not clearly defined, and are often complicated by difficulties defining an 'older' adult within the context of HNC. The World Health Organization

defines an older adult as someone over the age of 60. However, chronological age may not correlate to biological ageing due to multiple chronic conditions and/or functional reserve capacity.³⁸ There is a move to consider the concept of frailty and its measurement and influence on outcomes in treatment decision-making. Only two studies in this review used frailty as part of their assessment.^{13,14} Both used different tools, which is not unusual in the literature, making comparisons difficult. It is evident this needs further consideration and review.

Standard treatment for HNC comprises surgery and/or radiotherapy and/or chemotherapy. It has been shown that age should not be an influencing factor in decision-making for radiotherapy.³⁹ The use of chemotherapy is less clear, with older people considered to be at high risk for toxicity.^{40,41} Conversely, a recent review of 4042 people older than 70 years from the National Cancer Data Base confirmed an overall survival benefit of adding chemotherapy concurrently to irradiation, although the overall survival gain was limited to those not older than 81 years, with low comorbidity scores, and whether T1-2/N2-3 or T3-4/N0-3.⁴² Improvements in treatments and management enable clinicians to offer curative intent to older people. However, these are difficult decisions for those with frailty, due to uncertainty about treatment and symptom-burden, expectations, values and preferences.

There is a need to develop treatment decision aids, especially for older people, to help them and their carers balance the burden of treatment, independence, quality of life and quality of time in survivorship.

4.2 | Strengths and limitations

This systematic review uniquely focused on treatment priorities and treatment regret in adults >65 with a diagnosis of HNC and identified a small number of papers fitting these inclusion criteria. Although studies have reported treatment priorities and regret, few focus on older adults with HNC. The included papers were highly variable in location, treatment type, treatment intent, outcome measurement and time points of measurement; therefore, differences in treatment protocols and expectations should be considered across varied geographical health economies.

We encountered some methodological challenges in trying to extract meaningful and relevant data. Although studies were eligible for inclusion if the mean population studied was >65 years of age, following the initial search, it was noted some studies did separate their cohort into younger and older groups but did not meet our inclusion criteria as their mean age was <65. This further adds to the difficulties in studying this unique population due to the lack of dedicated research in older adult cohorts.

4.3 | Future research

Future research should focus on reviewing the treatment priorities and preferences of those aged 65 and older. It would be beneficial to understand further how these priorities and preferences influence

treatment decision-making to further inform treatment pathways in this unique cohort.

5 | CONCLUSION

This review illustrates the priorities of older people in addition to identifying factors influencing treatment regret. There is a paucity of research in this area, but the available evidence indicates that older adults have a higher preference for maintaining their independence when making decisions about treatment and decision regret is impacted by resultant frailty and depression. Research within this field is problematic as ageing is an individualised and highly variable process with no standardised method recording chronological age versus physiological age and the implications of this for treatment decisions. Clinicians should consider patient's social circumstances, pre-morbid status and priorities in maintaining independence and managing symptoms when making treatment decisions for this age group.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Emer Fahy. The first draft of the manuscript was written by Emer Fahy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/coa.14094>.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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