What Is the Psycho-oncologic (PsyO) Impact of Progression in Patients with Cancer? A Targeted Literature Review (TLR) to Assess the Available Data

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HTA231

Background

- Progression-free survival (PFS) is widely used to evaluate the efficacy of novel cancer therapies[1]
- However, the relevance of PFS to a patient's quality of life (QOL) and outcomes of psychologic symptoms associated with cancer (PsyO) has yet to be determined
  - PsyO symptoms—such as anxiety and depression, which are common comorbidities for patients with cancer—are often underdiagnosed and are associated with increased healthcare costs[2–4]

Objective

- To identify clinical studies reporting how disease progression affects PsyO outcomes in patients with cancer

Conclusions

- Although current evidence is limited, the available data demonstrate that disease progression is significantly associated with reduced QOL in patients across cancer types, validating the relevance of PFS to patient outcomes
- Although fear of progression is not directly related to the event of progression, the association it has with PsyO outcomes suggests that patients are concerned about disease progression and that it can translate into meaningful effects on psychological outcomes
- Further research is needed to investigate the relationship between PFS and PsyO outcomes

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Presented at the Professional Society for Health Economics and Outcomes Research (ISPOR) Europe 2023 Meeting; 12–15 November 2023; Copenhagen, Denmark.

Methods

- Randomised clinical trials, observational studies, and registries that reported PsyO outcomes, including QOL and fear of progression, published between January 2018 and January 2023 were identified by searching EMBASE
- A grey literature search, with no restriction on date of publication, was also conducted to identify additional studies from the following sources:
  - Congresses: the Professional Society for Health Economics and Outcomes Research, American Society of Clinical Oncology, and World Congress on Lung Cancer
  - Google Scholar
- Studies were selected by 2 independent reviewers based first on title and abstract (first pass) and subsequently on full text (second pass)
- Extraction was carried out by 1 reviewer, and quality was assessed by a second reviewer, with disagreements resolved by a third reviewer
- Studies were assessed for relevance using the selection criteria in **Table 1**

Table 1. Selection Criteria for the TLR

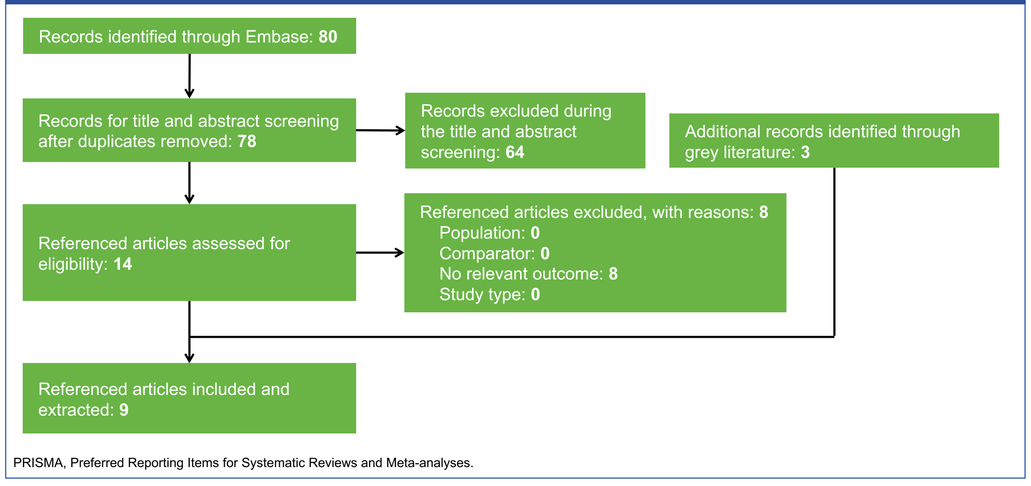
Selection criteria	Inclusion criteria	Exclusion criteria
Population	• People with cancer	• None
Interventions/ comparators	• Any	• None
Outcomes	• PsyO outcomes (eg, anxiety, depression, HRQOL, loss of control) reported either – A comparison of patients before and after disease progression – A comparison of patients with disease progression to those without	• Studies not reporting relevant outcomes
Study type	• RCTs • Observational studies • Registries	• Single-case reports • Reviews • Letters • Commentaries
Publication type	• Article, conference abstract, conference paper, article in press, poster	• Short survey, letter, editorial, review

HRQOL, health-related quality of life; PsyO, psycho-oncologic; RCT, randomised clinical trial; TLR, targeted literature review.

Results

- Eighty studies were identified through the Embase database search and 3 studies from the grey literature search (**Figure 1**)
- Following the removal of duplicates and articles excluded per **Table 1** exclusion criteria, a total of 6 studies from the Embase search and 3 studies from the grey literature search were included in this analysis (7 full papers, 2 abstracts)

Figure 1. PRISMA Flow Diagram for the Identification, Assessment, and Inclusion of Studies



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

- The study populations, outcomes, and key results from the 9 studies identified in the TLR are described in **Table 2**
- Five studies evaluated PsyO outcomes following disease progression
  - Three studies reported statistically significant decreases in QOL following disease progression, including emotional functioning and depression
    - Chase et al: statistically significant decreases in a number of QOL tools for patients with ovarian cancer after disease progression, especially in emotional functioning[6]
    - Marschner et al: statistically significant decreases in almost all QOL scales after first disease progression for patients with lung, breast, pancreatic, and colorectal cancers, including in psychological outcomes such as depression[8]
    - Müller et al: metastases in patients with breast cancer predicted significantly more decreases in QOL than in those without metastases[9]
  - Two studies reported worsening of PsyO outcomes with factors related to disease progression
    - Rabsahl et al: patients with metastases or unfavourable prognoses had higher anxiety and depression scores than those without[5]
    - McCarthy et al: emotional symptoms in children with cancer were significantly associated with a change in disease status and more recent disease progression[7]
  - Four studies reported that patients with cancer experienced fear of progression or cancer recurrence, with 3 reporting quantitatively that this had a negative effect on PsyO outcomes
    - Laisaar-Powell et al: qualitatively reported that fear of progression may be associated with anxiety in patients with lung cancer[10]
    - Meissner et al: fear of recurrence was associated with more time since radical prostatectomy in survivors of prostate cancer[11]
    - Lieb et al: higher depression and anxiety could be predicted by fear of progression in patients with uveal melanoma[12]
    - Maguire et al: fear of cancer recurrence was significantly associated with lower QOL in patients with prostate cancer[13]
  - However, there are some uncertainties in the results, suggesting fear of progression varies between individuals and is influenced by different factors
    - Meissner et al: fear of recurrence increased slightly during a 9-year period[11]
    - Lieb et al: anxiety, depression, and fear of progression outcomes did not differ between patients who knew their prognostic test result and those who did not[12]

Table 2. Key Results of TLR-Identified Studies

Citation	Study type	Population	Sample size	Relevant outcomes reported	PsyO outcomes related to progression as an event	PsyO outcomes related to fear of progression
Rabsahl 2023[5]						
Study details	Prospective	Uveal melanoma (no metastases or tumour recurrence) undergoing proton therapy	• Baseline: N=130 • 1-year follow-up: n=99 • 2-year follow-up: n=91	• PHQ-9 • GAD-7	✓	
Key result	• Patients with metastases or unfavourable prognoses had numerically higher anxiety and depression scores than those without – Metastases vs no metastases (mean [SD]) ▪ **Depression**: 5.33 (3.51) vs 3.66 (3.49); **anxiety**: 4.33 (4.04) vs 3.78 (3.53) – Unfavourable vs favourable prognoses (mean [SD]) ▪ **Depression**: 4.67 (3.79) vs 4.33 (3.93); **anxiety**: 7.67 (7.51) vs 2.83 (3.37)					
Chase 2022[6]						
Study details	Phase 3 RCT, post hoc analysis	Advanced ovarian cancer responsive to first-line platinum-based chemotherapy (PRIMA)	• Total: N=733 • Niraparib: n=487 • Placebo: n=246	• EORTC QLQ-C30 • EORTC-QLQ-OV28 • EQ-5D-5L • EQ-VAS • FOSI	✓	
Key result	• Patients with ovarian cancer had a significant decrease in QOL after disease progression • LSM change at EOT: FOSI score (−2.1 [P<0.0001]), EQ-5D-5L score (−4.6 [P<0.0001]), and EQ-5D-VAS score (−7.9 [P<0.0001]) • Of EORTC-QLQ-C30 domains, emotional function had the largest decline between the last visit before progression and EOT, with an LSM change of −10.5 (P<0.0001), and remained low throughout the 24-week follow-up – Worsening in global health and QOL index mean scores from before progression to EOT was seen in both treatment groups					
McCarthy 2021[7] (abstract only)						
Study details	RCT	Paediatric advanced cancer	• N=913	• PediQUEST Memorial Symptom Assessment Scale • Pediatric Quality of Life Inventory 4.0	✓	
Key result	• Emotional symptoms in paediatric patients with advanced cancer were significantly associated with more recent disease progression – A change in disease status in the past 10 days (P=0.006) – Less time since last disease progression (P=0.002)					
Marschner 2020[8]						
Study details	Observational	Metastatic breast, lung, pancreatic, or colorectal cancer (4 registries in Germany)	• N=2314	• FACT-G • HADS • EORTC QLQ-C30 • EORTC QLQ-C15-PAL	✓	
Key result	• Disease progression is associated with a deterioration in QOL among patients with metastatic breast, pancreatic, lung, and colorectal cancer – Statistically significant decreases in most QOL scales (37 out of 45) were seen after the first disease progression across all 4 cancers; for 17 of these scales, the worsening was clinically meaningful[a] – Further statistically significant decreases in most QOL scales (32 out of 45) were seen after the second disease progression; the scales showed clinically meaningful changes[a] – Statistically significant decreases in global QOL in all 4 cancers after the first progression and in all cancers except breast after the second progression					
Müller 2018[9]						
Study details	Observational	Metastatic breast cancer (PRAEGNANT registry)	• N=326	• EORTC QLQ-C30	✓	
Key result	• Significantly greater deterioration in QOL was seen in breast cancer patients with disease progression than in those without – In the constructed logistic model, QOL score at baseline was the strongest predictor for an MID in QOL. Patients with progression had significantly more MIDs than those without (OR=2.22 [95% CI, 1.04–4.73]; P=0.04) – Although the primary study aim showed an influence of progression on MID, there was no difference in mean differences of global QOL scores. Furthermore, all other differences in mean changes over time were not statistically significant with regards to the functional or symptom scales					
Laidsaar-Powell 2022[10] (abstract only)						
Study details	Observational	Lung cancer 3–24 months after completion of initial active treatment	• N=20	• Qualitative telephone interviews		✓
Key result	Some survivors of lung cancer reported fear of disease progression, and lost physical abilities caused sadness and anxiety					
Meissner 2021[11]						
Study details	Prospective longitudinal	Prostate cancer with primary RP treatment	• N=2417	• Fear of progression questionnaire short form		✓
Key result	• Fear of cancer recurrence is associated with increased time since RP in survivors of prostate cancer – After a mean time of 7.3 years after diagnosis and treatment (2010), 6.5% of survivors reported high levels of fear of cancer; in 2019, 8.4% of survivors reported high fear of cancer – A higher age at RP (P=0.004) and more years since RP (P=0.005) were both associated with a higher risk of fear of cancer 9 years later – Biochemical cancer recurrence (P=0.001) and anxiety (P<0.001) between RP and 2010 predicted higher fear of cancer 9 years later – Depression in 2010 was not associated with fear of cancer in 2019, but depression in 2019 was significantly associated with high fear of cancer in 2019 (P<0.001)					
Lieb 2020[12]						
Study details	Controlled prospective clinical observational	Uveal melanoma	• Observational group: n=85 • D3 (good prognosis) group: n=27 • M3 (poor prognosis) group: n=30	• Fear of progression questionnaire • HADS-D • Perceived Risk VAS • Resilience (SOC-13) • SF-12 (mental and physical) • General distress (distress thermometer)		✓
Key result	• Higher fear of disease progression predicted higher levels of anxiety and depression in patients with uveal melanoma – Fear of progression, depressive symptoms, and anxiety decreased over time for both patient groups who received prognostic results, and these findings did not differ significantly from the observational group – A higher depression score at the end of the study could be significantly predicted by lower resilience (P=0.023), higher fear of progression (P=0.010), lower physical QOL (P=0.022), and higher depression (P<0.001) at the beginning of the study – A higher anxiety score at the end of the study was significantly predicted by younger age (P=0.031), higher fear of progression (P=0.001), higher anxiety (P=0.039), and lower physical (P=0.042) and mental (P=0.043) QOL at the beginning of the study					
Maguire 2018[13]						
Study details	Retrospective and prospective questionnaire	Prostate cancer 25 years after diagnosis from the National Cancer Registry, Ireland	• N=817	• EORTC QLQ-C30 • 5-item fear of recurrence scale		✓
Key result	• Fear of cancer recurrence was the strongest factor associated with lower QOL in survivors of prostate cancer – The strongest associated factor with lower QOL was a higher fear of cancer recurrence (β=−0.29; P<0.001) – Having a later-staged disease was also significantly associated with lower QOL (β=−0.07; P=0.02)					

[a]Clinically meaningful defined as a decrease of ≥5%. D3, disomy; EORTC, European Organisation for the Research and Treatment of Cancer; EOT, end of treatment; EQ, EuroQol; FACT-G, Functional Assessment of Cancer Therapy–General; FOSI, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; GAD, generalised anxiety disorder; HADS, Hospital Anxiety and Depression Scale; LSM, least squares mean; M3, monosomy; MID, minimally important deterioration; OR, odds ratio; PHQ, Patient Health Questionnaire; QLQ, quality of life questionnaire; QOL, quality of life; RCT, randomised control trial; RP, radical prostatectomy; SOC, sense of coherence; SF-12, 12-item Short-Form Survey; VAS, visual analog scale.

Limitations of this analysis

- Only 9 studies were identified, of which detailed results were not available for 2. PsyO outcomes can be difficult to define because of the term's broadness, which may have led to relevant papers not identified in the search strategy or excluded from this TLR
- The research questions of studies included in this review differed substantially such that in some cases, results relating to secondary or tertiary objectives were extracted to supplement the TLR or some studies were included that were only loosely linked to the TLR
- Many different cancer types were studied in the identified papers, each with differing symptom burden and prognosis associated with progression. This heterogeneity may have been a factor for differing results amongst studies

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Acknowledgments

This study (214770) was funded by GSK (Waltham, MA, USA). Writing and editorial support, funded by GSK, were provided by Kristoffer Myczek, PhD, and Jennifer Robertson, PhD, of Ashfield MedComms, an Inizio company.

Conflicts of Interest

Manasee V. Shah and **Kelly F. Bell** are employees and shareholders of GSK. **Cianne Park**, **Ellen Codling**, **Owen Harrison**, and **Sabine Gaugris** are employees of FIECON Ltd.