Universidad de Oviedo

PROGRAMA DE DOCTORADO EN CIENCIAS DE LA SALUD

Título de la tesis:

Análisis Integral del Malestar Psicológico, Calidad de Vida y Conciencia Pronóstica en Pacientes con Cáncer Avanzado: Estudio Prospectivo NEOetic-SEOM

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Español/Otro Idioma: Análisis Integral del Malestar Psicológico, Calidad de Vida y Conciencia Pronóstica en Pacientes con Cáncer Avanzado: Estudio Prospectivo NEOetic-SEOM	Inglés: Comprehensive Study on Psychological Distress, Quality of Life, and Prognostic Awareness in Patients with Advanced Cancer: NEOetic-SEOM Study

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RESUMEN (en español)

Introducción

El cáncer, un problema sanitario creciente, influye de manera notable en las dimensiones físicas, emocionales y socioeconómicas de la vida del paciente. El progreso de la enfermedad a menudo provoca un deterioro de la calidad de vida, incrementando los síntomas físicos y psicológicos, especialmente en casos de neoplasias avanzadas.

Para mejorar la atención al paciente es esencial identificar qué aspectos físicos y psicológicos se ven más afectados y los factores clínicos y sociodemográficos que los modulan. Este análisis debe contemplar la estrategia de afrontamiento del paciente y la comunicación e interacción con su oncólogo.

Objetivos

Los cinco objetivos principales, uno por artículo son: 1) evaluar la prevalencia de fatiga, angustia e incertidumbre en cáncer metastásico y su influencia en la calidad de vida; 2) investigar la relación entre el estado general de paciente, su ajuste mental y la potencial aparición de depresión; 3) analizar cómo la información del oncólogo y la conciencia pronóstica impactan en los problemas psicológicos, afrontamiento y toma de decisiones del paciente; 4) discernir el impacto de los tratamientos antineoplásicos en la calidad de vida, contrastando cáncer resecado y avanzado y 5) validar una escala rápida y fiable para evaluar problemas psicológicos en pacientes con los cánceres avanzados más prevalentes (colorrectal y broncopulmonar).

Método

Este estudio se fundamentó en NEOetic, un registro prospectivo y multicéntrico de la Sociedad Española de Oncología Médica. Se utilizaron distintas escalas para valorar la calidad de vida, malestar psicológico, afrontamiento, incertidumbre y conciencia pronóstica en pacientes con cáncer avanzado irresecable. Además, se examinó su asociación con aspectos sociodemográficos, clínicos y de tratamiento.

Resultados

El primer estudio encontró una correlación entre fatiga, malestar psicológico e incertidumbre sobre la enfermedad con disminución de la calidad de vida en pacientes con cáncer avanzado.

El segundo trabajo mostró que la cantidad de síntomas se correlaciona con un peor estado funcional y más síntomas depresivos. Las estrategias de afrontamiento mediaban esta relación. Una actitud positiva podía reducir los síntomas de depresión.

El tercer análisis reveló que el 74% de los pacientes con cáncer avanzado incurable mantenía la creencia en la curabilidad y el impacto de la conciencia pronóstica en la aceptación del tratamiento, mostrando un interés creciente hacia terapias de baja eficacia, particularmente entre pacientes con un fuerte apoyo social, miedo a la muerte y creencia en la curabilidad.

En el cuarto estudio, encontramos que los pacientes con cáncer avanzado experimentaban una calidad de vida más pobre y una satisfacción con la vida más baja en comparación con los pacientes con cáncer localizado. Sin embargo, el deterioro en la calidad de vida durante el tratamiento fue mayor en cáncer resecado.

En el quinto estudio, proponemos subescala EF-EORTC-QLQ-C30, una herramienta sencilla y efectiva para detectar el malestar psicológico en pacientes con cáncer avanzado.

Conclusiones

1) La fatiga y el malestar psicológico se intensifican en pacientes con cáncer avanzado, deteriorando su calidad de vida.

2) El deterioro físico y las estrategias de afrontamiento negativas incrementan la depresión.

3) La consciencia pronóstica repercute en la toma de decisiones y el estado de ánimo.

4) El tratamiento antineoplásico preserva la calidad de vida en pacientes con cáncer avanzado mientras que la perjudica en enfermedad localizada

5) La subescalada EF-EORTC-QLQ-C30 es una herramienta rápida y eficaz para estudiar el malestar psicológico en pacientes con cáncer torácico o colorrectal avanzado.

Universidad de Oviedo

RESUMEN (en Inglés)

Introduction

Cancer, a growing health problem, significantly impacts the physical, emotional, and socioeconomic dimensions of a patient's life. The progression of the disease often leads to a deterioration in quality of life, increasing physical and psychological symptoms, especially in advanced neoplasm cases.

To improve patient care, it's essential to identify which physical and psychological aspects are most affected and the clinical and sociodemographic factors that modulate them. This analysis should consider the patient's coping strategy and communication and interaction with their oncologist.

Objectives

The five main objectives, one for each article, are: 1) to evaluate the prevalence of fatigue, distress, and uncertainty in metastatic cancer and its influence on quality of life; 2) to investigate the relationship between the patient's general state, their mental adjustment, and the potential onset of depression; 3) to analyse how the oncologist's information and prognostic awareness impact the patient's psychological problems, coping, and decision-making; 4) to discern the impact of antineoplastic treatments on quality of life, contrasting resected and advanced cancer, and 5) to validate a quick and reliable scale to evaluate psychological problems in patients with the most prevalent advanced cancers (colorectal and bronchopulmonary).

Method

This study was based on NEOetic, a prospective and multicentre registry of the Spanish Society of Medical Oncology. Various scales were used to assess the quality of life, psychological distress, coping, uncertainty, and prognostic awareness in patients with advanced inoperable cancer. Additionally, their association with sociodemographic, clinical, and treatment aspects was examined.

Results

The first study found a correlation between fatigue, psychological distress, and uncertainty about the disease with a decrease in the quality of life in patients with advanced cancer.

The second work showed that the number of symptoms correlated with a worse functional state and more depressive symptoms. Coping strategies mediated this relationship. A positive attitude could reduce depression symptoms.

The third analysis revealed that 74% of patients with incurable advanced cancer-maintained belief in curability and the impact of prognostic awareness on treatment acceptance, showing increasing interest in low-efficacy therapies, particularly among patients with strong social support, fear of death, and belief in curability.

In the fourth study, we found that patients with advanced cancer experienced a poorer quality of life and lower life satisfaction compared to patients with localized cancer. However, the deterioration in quality of life during treatment was greater in resected cancer.

In the fifth study, we propose the EF-EORTC-QLQ-C30 subscale, a simple and effective tool to detect psychological distress in patients with advanced cancer.

Conclusions

1) Fatigue and psychological distress intensify in patients with advanced cancer, deteriorating their quality of life.
2) Physical deterioration and negative coping strategies increase depression.
3) Prognostic awareness impacts decision-making and mood.
4) Antineoplastic treatment preserves the quality of life in patients with advanced cancer while it harms localized disease.
5) The EF-EORTC-QLQ-C30 subscale is a quick and effective tool to study psychological distress in patients with advanced thoracic or colorectal cancer.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN _____

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Dr. Emilio Esteban	Caterina Calderón	Elías Delgado
Director	Directora	Tutor

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LISTADO DE ABREVIATURAS

- SEOM: Sociedad Española de Oncología Médica
- STROBE: Strengthening the Reporting of Observational studies in Epidemiology
- EF-EORTC-QLQ-C30: Cuestionario de Calidad de Vida de la Organización Europea para la Investigación y el Tratamiento del Cáncer
- HHS: Herth Hope Scale
- SWLS: Escala de satisfacción con la vida
- BSI-18: Brief Symptom Inventory
- Mini-MAC: Mini-Mental Adjustment to Cancer
- MUIS: Michel Uncertainty in Illness Scale
- PDRQ-9: Patient-Doctor Relationship Questionnaire
- FACIT-Sp-12: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale
- Duke-UNC-11: Perceived Social Support Questionnaire
- SWD: Satisfaction With Decision
- CWQ-FoR: Cancer Worry Questionnaire
- NEOetic.EIT: Expectations Regarding Treatment Effectiveness NEOetic
- Preference On Information NEOetic
- NEOetic-IIT: Interest In Therapy NEOetic
- STAR-P: Scale to Assess the Therapeutic Relationship-Patients' version.
- ANOVA: análisis de varianza
- MANCOVA: Análisis Multivariante de Covarianza
- ECOG: Eastern Cooperative Oncology Group

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INDICE

1. PRESENTACION

Este trabajo es presentado con el objetivo de obtener el título de Doctor en Medicina y Cirugía por la Universidad de Oviedo. La investigación se llevó a cabo entre los años 2021 y 2023 en el Hospital Universitario Central de Asturias (Oviedo).

La tesis doctoral se compone de un conjunto de cinco artículos originales de investigación, publicados en 2022 y 2023, e indexados en el Journal Citation Reports (secciones Science Citation Index -SCI- y Social Science Citation Index -SSCI-).

La investigación doctoral se encuentra enmarcada en el estudio NEOetic, dirigida por la Dra. Caterina Calderón, psicóloga de la Universidad de Barcelona y el Dr. Emilio Esteban, jefe del servicio de Oncología Médica del Hospital Universitario Central de Asturias. Desde 2021, formo parte de dicho proyecto en calidad de investigador. El estudio NEOetic contó con el apoyo financiero de las becas FSEOM 2018, otorgada al mejor proyecto promovido por un grupo de trabajo de SEOM y por la beca nacional ASTRAZENECA 2020.

A continuación, se detallan las referencias de los cinco artículos incluidos en este compendio, los cuales serán referidos a lo largo del documento en el siguiente orden:

Artículo 1: **Rodriguez-Gonzalez A,** Velasco-Durantez V, Martin-Abreu C, Cruz-Castellanos P, Hernandez R, Gil-Raga M, et al. Fatigue, Emotional Distress, and Illness Uncertainty in Patients with Metastatic Cancer: Results from the Prospective NEOETIC_SEOM Study. Current Oncology 2022;29:9722–32. https://doi.org/10.3390/curroncol29120763.

Revista: Current Oncology, ISSN 1198-0052, EISSN 1718-7729. Edition: Science Citation Index Expanded (SCIE). Category: Oncology-SCIE. Languages: English. Región: Switzerland. 1ST Electronic JCR year: 2010.

JOURNAL IMPACT FACTOR: 3.109.

Artículo 2: **Rodríguez-González A,** Velasco-Durántez V, Cruz-Castellanos P, Hernández R, Fernández-Montes A, Jiménez-Fonseca P, et al. Mental Adjustment, Functional Status, and Depression in Advanced Cancer Patients. Int J Environ Res Public Health 2023;20:3015. https://doi.org/10.3390/ijerph20043015.

Revista: International Journal of Environmental Research and Public Health, EISSN 1660-4601. Edition: Social Sciences Citation Index (SSCI), Science Citation Index Expanded (SCIE). Category: Public, environmental & occupational health - SSCI. Languages: English. Región: Switzerland. 1ST Electronic JCR year: 2011

JOURNAL IMPACT FACTOR: 4.614

Artículo 3: Carmona-Bayonas A, **Rodriguez-Gonzalez A**, García-García T, Velasco-Durantez V, Hernández-San Gil R, Cruz-Castellanos P, ¿et al. Can Oncologists Prompt Patient Prognostic Awareness to Enhance Decision-Making? Data From the Neoetic Study. Oncologist 2023. https://doi.org/10.1093/oncolo/oyad100.

Revista: ONCOLOGIST, ISSN 1083-7159, EISSN 1549-490X. Edition: Science Citation Index Expanded (SCIE). Category: Oncology-SCIE. Languages: English. Región: USA. 1ST Electronic JCR year: 2003

JOURNAL IMPACT FACTOR: 5.837

Artículo 4: Rodríguez-Gonzalez A, Carmona-Bayonas A, Hernández San Gil R, Cruz-Castellanos P, Antoñanzas-Basa M, Lorente-Estelles D, et al. Impact of Systemic Cancer Treatment on Quality of Life and Mental Well-being: A Comparative Analysis of Patients with Localized and Advanced Cancer. Clinical and Translational Oncology 2023. DOI: 10.1007/s12094-023-03214-5

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Revista: Clinical & Translational Oncology, ISSN 1699-048X, EISSN 1699-3055. Edition: Science Citation Index Expanded (SCIE). Category: Oncology-SCIE. Languages: English. Región: Spain. 1ST Electronic JCR year: 2009

JOURNAL IMPACT FACTOR: 3.340

Artículo 5: **Rodriguez-Gonzalez A**, Hernández R, Cruz-Castellanos P, Fernández-Montes A, Castillo-Trujillo O, Muñoz MM, et al. Using the emotional functioning in clinical practice to detect psychological distress in patients with advanced thoracic and colorectal cancer. Health Qual Life Outcomes 2023;21:15. https://doi.org/10.1186/s12955-023-02099-w.

Revista: Health and Quality of Life Outcomes, EISSN 1477-7525. Edition: Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI). Category: Health policy & services – SSCI, Health care sciences & services - SCIE. Languages: English. Región: England. 1ST Electronic JCR year: 2008

JOURNAL IMPACT FACTOR: 3.007

2. INTRODUCCION

2.1 Calidad de vida en el paciente oncológico con cáncer avanzado

El cáncer constituye un problema de salud cada vez más relevante en nuestra sociedad, con una incidencia en constante crecimiento, registrando 19,3 millones a nivel mundial en 2020 y proyectándose en 28,9 millones para el año 2040 [1,2]. Simultáneamente, los avances en detección y tratamiento del cáncer han dado lugar a un aumento de la supervivencia de los pacientes, estimándose que la prevalencia de esta enfermedad aumentará hasta un 30% en la próxima década. Estas circunstancias generan un problema de alcance social que impacta física, emocional y socioeconómicamente a los pacientes, familiares y el conjunto de la sociedad.

Diversos estudios revelan que los pacientes con cáncer presentan un evidente deterioro de su calidad de vida en comparación con la población general desde el inicio de la enfermedad. Dicho deterioro se manifiesta en las primeras fases de tratamiento y persiste hasta el final de la enfermedad [3–5].

En el contexto de los pacientes oncológicos, la calidad de vida se entiende como un concepto dinámico y multidimensional, referido a todos los aspectos de la vida y necesidades del paciente. Dicha calidad de vida evalúa el equilibrio entre la situación real y la situación ideal en un momento determinado [6].

El deterioro de la calidad de vida en pacientes oncológicos es atribuible al proceso de la enfermedad en sí, al tratamiento y a su duración, la cual suele ser indefinida en pacientes con una enfermedad avanzada e irresecable [7]. Los múltiples problemas somáticos, emocionales y socioeconómicos que desarrollan los pacientes en las diferentes etapas de la enfermedad contribuyen a dicho deterioro.

2.1.1 Síntomas somáticos

Los pacientes con cáncer avanzado experimentan numerosos síntomas somáticos persistentes, molestos e intensamente limitantes. Diversos estudios han demostrado que estos síntomas se asocian a una mayor discapacidad y menor calidad de vida, con una mayor prevalencia en pacientes con enfermedades avanzadas y tratamientos prolongados [8,9].

Estos estudios muestran como los pacientes oncológicos sufren un deterioro del estado funcional que limita sus actividades físicas diarias debido a la presencia de numerosos síntomas somáticos [7]. El dolor afecta hasta al 72% de los pacientes [10], mientras que otros presentan disnea, pérdida de peso, falta de apetito (en hasta en el 71% de los casos [11], estreñimiento, náuseas y vómitos (en hasta un 60% de los pacientes [12], trastornos del sueño (en hasta un 38%) y fatiga generalizada, presente en el 90% de los pacientes, especialmente en fases avanzadas del cáncer [13,14].

La frecuencia de estos síntomas varía en función del tipo de cáncer, viéndose como en los pacientes con cáncer de pulmón presentan mayores tasas de disnea, fatiga y tos [15] , mientras que en los de origen gastrointestinal es más frecuente el dolor, la pérdida de peso y la fatiga [16], y en aquellos de origen ginecológico o de mama, se presentan con mayor frecuencia síntomas como alteraciones sexuales y fatiga, además de síntomas psicoafectivos [17,18].

Uno de los síntomas más frecuentes y menos estudiados es la fatiga, la cual hasta hace poco solía ser subestimada al enfocarse más atención en síntomas como las náuseas y el dolor [19,20]. La fatiga puede pasar desapercibida debido a diversos factores que contribuyen a su desarrollo y enmascaramiento, como el síndrome general del cáncer, efectos directos de la neoplasia o su tratamiento sobre el sistema nervioso central o el metabolismo energético muscular, trastornos del sueño o ritmos circadianos, estrés, desánimo o depresión, activación inmunitaria,

anemia, caquexia o desnutrición, entre otros [21,22]. A pesar de su alta prevalencia y su posible interferencia con las actividades y el bienestar de los pacientes, la investigación sobre la etiopatogenia y el abordaje de la fatiga sigue siendo insuficiente en pacientes con cáncer metastásico.

La fatiga afecta a pacientes independientemente de su edad, sexo, tipo de cáncer, etapa de la enfermedad y modalidad de tratamiento [23–25]. Puede hacerse persistente y limitar la calidad de vida y las actividades cotidianas de los pacientes durante años [12,26]. Además, la fatiga asociada al cáncer difiere del agotamiento que la mayoría de las personas experimentan como resultado de sus actividades diarias, ya que no es proporcional al nivel de esfuerzo realizado y el descanso o el sueño no logran aliviarla [12,25]. La fatiga no sólo deteriora la calidad de vida, sino que también restringe las actividades físicas y sociales del paciente y su capacidad para reincorporarse al ámbito laboral.

2.1.2 Aspectos psicosociales

El cáncer también lleva consigo implicaciones psicológicas y psicosociales significativas, evidenciando un marcado deterioro en los pacientes en comparación con la población general. Un estudio que incluyó a 768 pacientes con cáncer mostró que el 98,3% experimentaba malestar psicológico en sus interacciones sociales [10], lo cual es indicativo de los retos psicosociales que conlleva la enfermedad.

Los pacientes oncológicos, especialmente aquellos en etapas avanzadas, presentan una alta prevalecía de malestar emocional. Aunque las cifras varían según el grupo de edad y el tipo de cáncer, se identifican problemas emocionales en más del 30% de los pacientes [27]. Este malestar emocional suele asociarse con cinco síntomas clave: ansiedad, depresión, miedo a la muerte, desmoralización e incapacidad para enfrentar la enfermedad.

La depresión y la ansiedad son los dos síntomas más prevalentes dentro de estos cinco, con tasas de depresión en pacientes oncológicos que varían entre el 18% y el 67% y tasas de ansiedad entre el 6.5% y el 23% [28–31]. La depresión, caracterizada por una sensación constante de desaliento; se asocia con una disminución en la funcionalidad, menor adherencia al tratamiento, hospitalizaciones más largas y una tasa de supervivencia más baja [32–34], lo que requiere una creciente atención y soporte por parte de los médicos e investigadores.

La depresión se presenta en diferentes grados, influida por una variedad de factores, incluyendo la reacción al diagnóstico de cáncer, los síntomas secundarios al tumor, el tratamiento y la incertidumbre en torno a la progresión de la enfermedad [35,36]. Varios factores psicosociales y demográficos, como la edad, el sexo, el tipo de tumor y el curso de la enfermedad tienen influencia en la depresión de estos pacientes [37,38].

Una revisión sistemática de 40 artículos sugirió que las mujeres son más propensas a la depresión que los hombres [39,40]; y en términos de edad, se ha observado que los sujetos oncológicos más jóvenes presentan más síntomas depresivos que los mayores, aunque los resultados no son concluyentes [13]. En cuanto a los factores físicos, las personas con comorbilidades y otras condiciones crónicas tienen un mayor riesgo de depresión, al igual que aquellos con metástasis [41]. En los casos de cáncer avanzado, los sujetos más jóvenes y las mujeres tendían a presentar más síntomas de depresión que los hombres y las personas mayores [31,41].

El estado físico y funcional son particularmente relevantes, ya que su deterioro se correlaciona con un aumento de los síntomas psicológicos, incrementando el riesgo de trastornos del estado de ánimo y reduciendo la calidad de vida [42]. Este estado funcional, que ha sido reconocido durante mucho tiempo como un

predictor del resultado del cáncer [43] está determinado por la extensión de los síntomas del cáncer, las comorbilidades que presentan estos pacientes, su habilidad para realizar las actividades diarias y cuánta ayuda necesitan para el autocuidado básico.

Muchos estudios confirman la importancia del estado funcional como predictor de supervivencia en casos de enfermedad avanzada [44–46]. Aquellos pacientes cuyo estado funcional ha sufrido un deterioro toleran peor los tratamientos contra el cáncer [47,48] y presentan una evolución de la enfermedad más desfavorable en comparación con otros pacientes en el mismo estadio de cáncer [49,50]. En este contexto, las estrategias de afrontamiento pueden desempeñar un papel esencial como mediadoras entre el estado funcional y los síntomas depresivos.

Junto con estos síntomas, la población referida también presenta alta prevalencia de trastornos adaptativos, miedo e incertidumbre acerca de la enfermedad y su pronóstico, así como una insatisfacción vital significativa [51,52].

Todo lo anterior tiene un impacto directo, dando lugar a una disminución en la calidad de vida, un empeoramiento en el estado funcional, un aumento en la tasa de suicidio y una muerte prematura en la población estudiada [53].

Identificar los factores asociados con la depresión puede proporcionar una base para la intervención y el tratamiento. Al hacerlo, es posible reducir la prevalencia de síntomas psicosociales en nuestros pacientes, lo que repercutirá en una mejor calidad de vida.

2.1.3 Incertidumbre sobre la enfermedad y estrategias de afrontamiento

Dada la gravedad del diagnóstico y la complejidad de la patología, los pacientes con cáncer suelen experimentar una profunda incertidumbre sobre su

enfermedad y la evolución de esta, la cual llega a afectar hasta el 60% de ellos [54]. Esta incertidumbre puede hacer que el paciente experimente una sensación persistente de pérdida de control, repercutiendo negativamente en como el paciente se enfrenta al cáncer, en su bienestar psicológico y en su calidad de vida.

La incertidumbre en pacientes con un cáncer avanzado e irresecable surge de la incapacidad de predecir con certeza la evolución de la neoplasia, la percepción amenazante del futuro, la situación avanzada del proceso, y/o las barreras en la comunicación (conspiración del silencio, bloqueo emocional, nivel cultural, habilidad del profesional, entre otros).

Numerosos estudios han vinculado la presencia de incertidumbre clínica con deterioro en la calidad de vida y en la resiliencia, así como con un aumento de la ansiedad y depresión. Se ha observado como dicha incertidumbre sobre la enfermedad puede desencadenar problemas psicológicos en los pacientes, los cuales padecen malestar psicológico en hasta un 30-50% de los casos [55–58].

Esta incertidumbre y los problemas psicológicos que desencadena están moldeados por el ajuste mental del paciente, entendido este como las respuestas cognitivas y conductuales de la persona a su diagnóstico de cáncer [59]. Los estilos de afrontamiento activos y positivos ante el cáncer se correlacionan con una mejor adaptación mental frente a la enfermedad, mejor adherencia al tratamiento y calidad de vida, reforzando así el sentido de autoeficacia y control personal del paciente [49,60,61]. Por el contrario, el afrontamiento evitativo del cáncer, la desesperanza, la preocupación ansiosa o la presencia de emociones negativas aumentan los síntomas depresivos en las personas con cáncer y se vinculan a una mentalidad sombría y negacionista sobre su cáncer, provocando un estrés constante y mayor dificultad para emprender acciones de resolución y asimilación, pudiendo incluso influir en la evolución de la enfermedad [62,63].

Si bien el concepto de incertidumbre sobre la enfermedad está claramente relacionado con aumento de síntomas psicológicos, la conciencia pronóstica no siempre muestra una mejoría, entendiéndose ésta como un fenómeno multifactorial en el que deben entrelazarse consideraciones culturales y circunstancias individuales [64].

Parte de este problema se asocia con dificultades para transmitir la información adecuada. Si bien no todos los pacientes desean conocer con detalle su enfermedad, la toma de decisiones compartidas entre paciente y médico sobre esta debe basarse en expectativas realistas entorno a la misma, expectativas que no serán realistas sin una información completa [65,66].

Sin embargo, se deben superar muchos obstáculos en esta situación. No es raro que exista una conspiración de familiares o médicos para ocultar información. En consecuencia, muchos sujetos con enfermedades incurables y progresivas como el cáncer albergan expectativas poco realistas y concepciones erróneas con respecto a los objetivos del tratamiento y a menudo se encuentran incapaces de discernir si el objetivo es curativo o meramente paliativo, es decir, si se busca prolongar la supervivencia global [67–71].

Por ejemplo, en el estudio *"Cancer Care Outcomes Research and Surveillance (CanCORS)"*, se halló que el 69 % y el 81 % de los pacientes con cáncer metastásico de pulmón y colon, respectivamente, tenían la creencia de la potencial curabilidad de su cáncer [67]. Los autores concluyeron que el malentendido en torno al pronóstico obstaculizaba la toma de decisiones basadas en las preferencias de los pacientes, lo que en casos extremos podría llegar a afectar la validez del consentimiento informado [72,73].

Una posible interpretación sería que lograr percepciones realistas sobre los medicamentos antineoplásicos teóricamente podría disminuir el uso de

tratamientos y acciones que probablemente no mejorarían la calidad de vida y no cambiarían drásticamente la supervivencia de los pacientes [74].

Sin embargo, el desafío radica en que transmitir un pronóstico tan crudo como una sentencia de muerte demanda tiempo, ya que inevitablemente desencadenará sufrimiento psicológico y comprometerá la calidad de vida de nuestros pacientes [75,76]. Cuando se les consulta, la mayoría de los pacientes manifiestan que quieren recibir información veraz que les permita participar en la toma de decisiones, pero al mismo tiempo necesitan aferrarse a la esperanza y consideran que la información abrupta carece de compasión [77].

En términos pragmáticos, esto significa que la información no puede forzarse precisamente en el momento en que se necesita para decidir sobre el tratamiento; por ende, debe ponderarse el momento de la divulgación completa de información. Esta deliberación debe ser breve, si se quiere que la eficacia del tratamiento no se vea comprometida. No obstante, el desarrollo de estrategias de afrontamiento adaptativas tiende a llevar tiempo; por lo tanto, proporcionar información más completa podría retrasar el tratamiento o tener consecuencias para el bienestar mental del paciente.

Si bien la incertidumbre respecto a la enfermedad oncológica puede llegar a repercutir en la calidad de vida de los pacientes, la entrega forzada de información también lo puede hacer, planteando un dilema ético al oncólogo a la hora de transmitir la información y las consecuencias que está tendrá en el paciente, todo ello modulado por las estrategias de afrontamiento que este adopte.

2.2 Influencia de la calidad de vida

Los profesionales dedicados al tratamiento de pacientes con cáncer persiguen la optimización del abordaje terapéutico de este, intentando controlar los síntomas somáticos y psicosociales provocados por la enfermedad y el tratamiento antineoplásico. Todo ello se orienta a mejorar la supervivencia y calidad de vida de esta población. En el caso de los pacientes con cáncer avanzado, dada la naturaleza en gran medida incurable de la enfermedad, el incremento de la calidad de vida se torna uno de los objetivos más importantes a perseguir.

Esta calidad de vida no solo conlleva una mejor tolerancia al proceso y a los tratamientos, sino que, en el caso de los pacientes con enfermedad avanzada, se ha visto relacionada con un mejor pronóstico de su enfermedad [78,79]. Si bien en las últimas décadas este objetivo ha cobrado mayor relevancia en la conciencia de los oncólogos, existe la percepción de una insuficiencia de herramientas objetivas, validadas y aplicables en la práctica clínica diaria que permitan valorar la calidad de vida y los síntomas asociados a esta en el paciente con cáncer.

Para el oncólogo, este desafío radica en que, por lo general, dispone de un tiempo limitado para atender al paciente durante las visitas clínicas y debe valorar una gran cantidad de síntomas y complicaciones asociadas al cáncer y su tratamiento, lo que a menudo dificulta la adopción de un enfoque integral y eficaz en el ámbito psicológico. Por otro lado, debido a su estado físico y psicológico general, las personas con cáncer avanzado tienen una capacidad de concentración y respuesta a cuestionarios más limitada que la población general.

Ante la complejidad y trascendencia de la calidad de vida en el marco de la atención oncológica a pacientes con cáncer avanzado e irresecable, resulta esencial profundizar en la comprensión de aquellos factores que contribuyen tanto a su deterioro como a su potencial mejora. Es por eso que este estudio se propone enfrentar esta problemática desde una visión integradora y

multidimensional. Con un enfoque integral y meticuloso, nos centramos en esclarecer los factores esenciales que inciden en la calidad de vida de los pacientes oncológicos. Este abordaje contempla desde el estado físico y emocional de los pacientes, pasando por las implicaciones del tratamiento antineoplásico, hasta la transmisión de información por parte del oncólogo. Esta perspectiva holística nos permite la creación de un marco de referencia más completo, y, como meta final, propiciar la instauración de intervenciones más eficaces y personalizadas destinadas a mejorar la calidad de vida de estos pacientes.

3. OBJETIVOS

Los objetivos específicos de esta tesis se dividen de acuerdo con los cinco artículos que la componen:

1) El primer objetivo es determinar la prevalencia de la fatiga, el malestar emocional y la incertidumbre sobre la enfermedad en pacientes con cáncer avanzado e irresecable, así como su valor predictivo en relación con el deterioro de la calidad de vida.

2) En el segundo artículo, el objetivo es establecer la relación entre el estado general del paciente y su ajuste mental con la depresión que puede desarrollar a lo largo de su enfermedad.

3) El tercer objetivo, derivado del tercer artículo, es explorar cómo la información proporcionada por el oncólogo médico influye en la conciencia pronóstica y en el proceso de la enfermedad, en términos de los problemas psicológicos que puede desarrollar el paciente, su afrontamiento y la influencia en la toma de decisiones.

4) En el cuarto artículo, buscamos discernir el impacto de los tratamientos antineoplásicos en la calidad de vida del paciente oncológico, analizando las diferencias entre la población con cáncer avanzado e irresecable con otra con un cáncer resecado con intención curativa.

5) El quinto objetivo es validar una escala rápida y fiable para evaluar problemas psicológicos en pacientes con los cánceres más prevalentes en nuestra muestra (colorrectal y torácico), con el fin de proporcionar una herramienta sencilla y eficaz para su uso en la práctica clínica diaria.

4. HIPOTESIS

De acuerdo con los objetivos de cada artículo se plantearon las diferentes hipótesis:

1) Esperamos encontrar altos niveles de fatiga, malestar emocional e incertidumbre sobre la enfermedad en nuestra muestra, observando como repercuten en un detrimento de la calidad de vida.

2) Se busca una relación entre el mal estado funcional y el empeoramiento de los síntomas depresivos, variando estos en función de las estrategias de afrontamiento que realicen los pacientes.

3) Se espera encontrar como una mayor información al paciente provoca una mayor consciencia pronóstica en los pacientes, influyendo en los problemas psicológicos que puedan desarrollar.

4) La hipótesis de este artículo buscaba relacionar el tratamiento quimioterápico con un empeoramiento de calidad de vida en el paciente oncológico y los síntomas que presenta.

5) La quinta hipótesis sugiere que la subescala EF-EORTC-QLQ-C30 es una herramienta fiable y rápida para realizar un cribado de los pacientes con malestar psicológico.

5. METODOLOGIA

5.1 Diseño del estudio

El cuerpo de esta tesis se deriva del estudio prospectivo y consecutivo NEOetic realizado en 15 hospitales de España desde febrero de 2020 hasta diciembre de 2022. Previo a la firma del consentimiento informado, se invitó a todos los pacientes adultos con un diagnóstico histológico confirmado de neoplasia avanzada, que estaban siendo atendidos en los servicios de oncología médica de estos hospitales, a participar de manera consecutiva en dicho estudio durante su primera visita al oncólogo.

Los procedimientos de recopilación de datos fueron similares en todos los hospitales y los datos relacionados con los participantes se obtuvieron de las instituciones e historias clínicas donde se administró el tratamiento. La participación en la investigación fue voluntaria, anónima y no afectó a la atención del paciente.

El protocolo de investigación comprendió la cumplimentación de varios cuestionarios por el paciente en su domicilio después de la primera entrevista clínica y antes de la administración del tratamiento antineoplásico sistémico en el mes siguiente al diagnóstico del cáncer. También se solicitó la cumplimentación de diversos cuestionarios tras el primer estudio de imagen para evaluar la respuesta al tratamiento. Además, se realizó una recopilación de datos clínicos durante la entrevista con el paciente y a través de su historia médica.

Los datos se recolectaron y actualizaron por el oncólogo médico a través de una plataforma web (www.neoetic.es).

Para el **cuarto artículo,** se utilizó el registro NEOcoping, con características similares al previo, aunque enfocado en pacientes con enfermedad localizada y resecada. El estudio comprendió la cumplimentación de varios cuestionarios por el paciente en su domicilio en el mes siguiente a la cirugía y tras la primera visita al oncólogo en la cual se le informó sobre la posibilidad de recibir tratamiento

antineoplásico complementario y se tomó una decisión compartida sobre la conveniencia de dicho tratamiento. Los cuestionarios los volvieron a cumplimentar tras finalizar el tratamiento oncológico adyuvante, aproximadamente a los 6 meses del inicio.

Los datos clínicos fueron recogidos y actualizados por el oncólogo, a través de una plataforma web www.neocoping.es. La ejecución de este estudio siguió las directrices de las guías *STROBE* [80].

5.2 Población de estudio

La población de estudio en NEOetic consistió en todos los pacientes con una neoplasia avanzada irresecable valorados para inicio de tratamiento antineoplásico en los servicios de oncología médica. Se excluyeron los pacientes candidatos a cirugía u otras terapias con intención curativa, aquellos que por sus condiciones físicas, comorbilidades y/o edad presentaban una contraindicación, para recibir tratamiento antineoplásico según criterio del oncólogo responsable, así como aquellos que hubieran recibido tratamiento oncológico en los dos años anteriores por otro cáncer avanzado, o con una situación personal, familiar, sociológica, geográfica y/o médica subyacente que pudiera obstaculizar la capacidad del paciente para participar en el estudio.

Por otra parte, en el estudio NEOcoping se incluyeron los pacientes con cáncer localizado resecado que precisaban de tratamiento antineoplásico complementario. Se excluyeron a los pacientes menores de 18 años, los que habían sido tratados con radioquimioterapia preoperatoria, terapia hormonal o radioterapia adyuvante sola (sin quimioterapia), y aquellos que padecían alguna enfermedad mental grave que les impidiese entender la naturaleza del estudio.

5.3 Descripción de variables

Los detalles sociodemográficos de los participantes en el estudio, como su edad, género, ocupación, nivel de educación, estado civil y lugar de residencia se recopilaron a través de un formulario estandarizado que cada paciente completó.

En cuanto a la información clínica, los datos relativos a la enfermedad de los participantes fueron recogidos por el oncólogo a cargo, quien revisó cada historial clínico. Este proceso aseguró la precisión y el detalle de los datos, que incluyen la localización del tumor primario, el tipo histológico del mismo, la presencia de biomarcadores moleculares, el estadio de la enfermedad al inicio del tratamiento, el tipo de terapia antineoplásica sistémica prescrita, el estado general del paciente y la finalidad de su tratamiento.

Los cuestionarios cumplimentados por el paciente se describen a continuación. Cada uno de estos cuestionarios ha sido validado en español [43,81,82].

El cuestionario EORTC-QLQ-C30 [83] incluye 30 elementos en cinco escalas funcionales (física, de rol, cognitiva, emocional y social), tres escalas de síntomas (fatiga, dolor, náuseas y vómitos), una escala de calidad de vida/estado de salud global y varios elementos individuales que evalúan síntomas adicionales comúnmente informados por pacientes con cáncer (disnea, pérdida de apetito, insomnio, estreñimiento y diarrea), y el impacto financiero percibido de la enfermedad. Las puntuaciones de cada elemento oscilan entre 0 y 100. Todas las puntuaciones de escala se transforman linealmente a una escala de 0 a 100. Las puntuaciones más altas en las escalas de funcionamiento representan un mayor nivel de funcionamiento. Para las escalas de síntomas, cuanto mayor sea la puntuación, mayor será la carga de síntomas.

La escala de satisfacción con la vida (SWLS) consta de 5 ítems y evalúa el juicio global de un individuo respecto a su satisfacción con la vida [84]. Se solicitó a los participantes que calificaran su grado de acuerdo con las afirmaciones utilizando

una escala Likert de siete puntos. Las puntuaciones totales oscilaron entre 5 y 35, y las puntuaciones más altas indicaban un nivel de satisfacción con la vida superior. En términos de confiabilidad, la consistencia interna de la escala fue bastante alta con un α=0.91 [85].

El cuestionario de síntomas psicológicos (BSI-18) evalúan el ajuste emocional general o el malestar psicológico en la última semana a través de 18 ítems [86]. Cada ítem se valora en una escala Likert de 5 puntos, desde 0 (nada) hasta 4 (extremadamente). El alfa de Cronbach está entre 0,81 y 0,90 [86].

La escala Mini-MAC es un cuestionario de 29 elementos que evalúa estrategias de afrontamiento específicas para el cáncer, clasificándolas como adaptativas (evitación cognitiva, espíritu de lucha) o maladaptativas (desesperanza, preocupación ansiosa y fatalismo). Al estudiar las propiedades psicométricas de la escala traducida al español, descubrimos una estructura de cuatro factores que se utilizó en este estudio e incluye tres subescalas del cuestionario original: desesperanza, preocupación ansiosa y evitación cognitiva, más una nueva subescala, actitud positiva, que incorpora el espíritu de lucha y el fatalismo [87]. El rango de fiabilidad de la escala oscila entre 0.83 y 0.89 [88].

La escala de Incertidumbre de la Enfermedad de Michel (MUIS) de 5 ítems y validada para población española [89–91] evalúa las reacciones ante la incertidumbre, las situaciones ambiguas y el futuro. Los ítems se puntúan en una escala Likert que va de 1 (el paciente no presenta ninguna de las características descritas en el ítem en absoluto) a 5 (el paciente presenta el mayor grado de la característica descrita), lo que arroja puntuaciones de 5 a 25, con puntuaciones más altas indicando más incertidumbre. El alfa de Cronbach fue de 0,83 [89].

La escala de la relación paciente-médico (PDRQ-9) consta de 9 ítems que evalúan la percepción de los pacientes sobre su relación con el oncólogo [92]. Su rango de fiabilidad oscila entre 0.81 y 0.92 [93].

Para el **tercer artículo**, se emplearon distintos cuestionarios que abarcan diversas facetas del bienestar del paciente, su relación con la enfermedad, su conciencia pronóstica y sus expectativas respecto al tratamiento. Entre ellos, se incluye la FACIT-Sp-12, que valora el bienestar espiritual en el entorno de una enfermedad crónica, ofreciendo información acerca de la relación entre espiritualidad, salud y calidad de vida [94,95]. El cuestionario Duke-UNC-11 se utiliza para medir la percepción de apoyo social que los pacientes sienten que reciben, un factor crucial en su habilidad para lidiar con la enfermedad [96,97]. La escala HHS es un instrumento que evalúa la esperanza y sus componentes en personas con enfermedades crónicas, incluyendo el cáncer [98]. La esperanza puede influir positivamente en cómo los pacientes enfrentan su enfermedad y tratamiento. Por otro lado, el cuestionario SWD examina la satisfacción del paciente con las decisiones de tratamiento tomadas, lo que es esencial para su adherencia al mismo [99]. El cuestionario CWQ-FoR mide el nivel de preocupación que los pacientes tienen respecto al cáncer, un factor que puede afectar a su calidad de vida y estado de ánimo [100]. Las siguientes tres escalas fueron creadas específicamente para este estudio y se validaron en una muestra inicial. El cuestionario NEOetic-EIT indaga las expectativas del paciente acerca de la eficacia del tratamiento, que puede influir en su compromiso y adherencia. La escala NEOetic-POI mide el deseo de los pacientes de obtener información sobre su enfermedad, pronóstico y tratamiento. El cuestionario NEOetic-IIT explora el interés y la motivación del paciente para participar activamente en su terapia según las expectativas de efectividad medidas como meses de vida ganados para supervivencia. Finalmente, la escala STAR-P evalúa la relación terapéutica desde la perspectiva del paciente [101].

5.4 Aspectos éticos

Esta investigación se ha llevado a cabo siguiendo los lineamientos de la Buena Práctica Clínica y la Declaración de Helsinki, y ha obtenido la aprobación del

Comité de Ética de Investigación de todas las Comunidades Autónomas y hospitales involucrados. El Comité referente fue el del Principado de Asturias, otorgando su aprobación el 17/05/2019 **(Anexo 2).**

La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) clasificó el estudio como un estudio observacional que no requiere de postautorización (no-EPA), registrado bajo el código de identificación: ES14042015, con fecha de 08/05/2019 **(Anexo 3).**

Se garantizó la plena comprensión y consentimiento de los participantes en la investigación, estableciéndose como condición necesaria que cada uno otorgase su aprobación, de manera consciente y por escrito, antes de su incorporación al estudio **(Anexo 4).**

5.5 Análisis estadístico

Los análisis estadísticos se realizaron con el software Statistical Package for Social Sciences (SPSS), versión 25.0 (IBM SPSS Statistics para Windows, Armonk, NY: IBM Corp) excepto los del cuarto artículo que se llevaron a cabo mediante R v4.05 incluyendo la librería brms.

5.5.1 Artículo 1

Se calcularon estadísticas descriptivas, medias y desviaciones estándar para las características demográficas y clínicas de la muestra. Se utilizó chi-cuadrado bivariado para evaluar las diferencias entre la fatiga y la angustia emocional según el sexo y el estadio de la enfermedad. Se calculó el coeficiente de correlación de Pearson para evaluar la asociación de la calidad de vida con fatiga, angustia emocional e incertidumbre de la enfermedad.

La multicolinealidad entre las variables fue rechazada por el factor de inflación de la varianza que fue <5 para todas y la tolerancia> 0,2 [102]. Para conocer la

variable predictiva de la calidad de vida se realizó un modelo de regresión lineal de dos bloques. En el primer bloque, la fatiga, la angustia emocional, la incertidumbre de la enfermedad se registraron como variables de criterio.

En el segundo bloque, se introdujeron el sexo y la edad como variables independientes. Aplicamos R-cuadrado y la medida estandarizada f2 de Cohen del tamaño del efecto para interpretar los datos. Para todos los análisis, la significancia se estableció en α <0,05.

5.5.2 Artículo 2

Se calcularon estadísticas descriptivas, medias y desviaciones estándar para las características demográficas y clínicas de la muestra. Se utilizó ANOVA para examinar las diferencias en los síntomas depresivos en función de las variables demográficas y clínicas. Se calculó eta cuadrada (η2) para evaluar el tamaño del efecto de las variables continuas. Eta-cuadrado varió de 0 a 1, con η2~0.01, η2~0.06 y η2 > 0.14 para un tamaño de efecto pequeño, mediano y grande, respectivamente.

Se utilizaron correlaciones bivariadas para evaluar la asociación entre la escala funcional y de síntomas (EORTC-QLQ-C30), las estrategias de afrontamiento (Mini-MAC) y la depresión (BSI). Todos los datos fueron estudiados por normalidad, valores atípicos y los supuestos de multicolinealidad y homocedasticidad. Se empleó el Modelo de Ecuaciones Estructurales (SEM) que es capaz de construir, estimar y probar modelos teóricos de las relaciones entre variables y que puede sustituir la regresión múltiple y otros métodos para analizar la fuerza de las correlaciones entre indicadores de variables individuales en una población específica.

En este estudio, se emplearon en el SEM factores significativos determinados previamente se utilizaron para identificar la relación entre la escala de síntomas y funcional, las estrategias de afrontamiento y la depresión. Los efectos directos,

indirectos y totales estandarizados con los correspondientes intervalos de confianza (IC) del 95% corregidos por sesgo se midieron utilizando los métodos de remuestreo. El ajuste del modelo se probó por medio del valor normado de $\chi 2$ (NC; valor deseado < 2.0, significado deseado $p < 0.05$), el índice de bondad de ajuste, el índice de ajuste comparativo (CFI), el índice de Tucker-Lewis (TLI), el índice de ajuste (NFI) (>0,95 que indica un ajuste excelente) y la raíz cuadrada media de aproximación (RMSEA; valor deseado $< 0,06$). La significación estadística bilateral se fijó en $p < 0,05$ para todas las pruebas.

5.5.3 Artículo 3

Para modelizar los objetivos se usaron regresiones ordinales con una función de enlace logit [103]. Los predictores se seleccionaron teóricamente, tras alcanzar un consenso entre los expertos del proyecto, y revisar sistemáticamente la literatura existente. Se consideró el juicio cualitativo de varios estudios, utilizando criterios de consistencia, plausibilidad teórica, causalidad y ausencia de ambigüedad temporal. Se respetó la estructura ordinal de las variables de respuesta.

Para los predictores ordinales se asumió que los efectos eran monótonos (es decir., consistentemente positivos o negativos a lo largo del espectro completo de la variable ordinal), si bien la magnitud de los cambios podía variar entre las categorías ordinales (no hubo asunción de equidistancia). Esta parametrización se realizó de la siguiente manera: un parámetro β recogió la dirección y el tamaño del efecto de forma similar a cualquier parámetro de regresión ordinario (es decir, cambio promedio en la variable de respuesta asociado a un incremento en la categoría del predictor), mientras que un vector de parámetros adicional, ζ también llamado parámetro simplex, estimó las distancias normalizadas entre categorías consecutivas del predictor. Por ejemplo, un parámetro ζ de 0.7 entre las dos últimas categorías del predictor indica que el 70% del efecto entre la categoría mínima y máxima reside en esas dos últimas categorías. El efecto no-

lineal de la edad se modelizó con una spline natural. Este modelo se implementó bajo una estructura bayesiana con 4 cadenas, cada una con 5000 iteraciones, y un periodo de calentamiento de 2500. Los gráficos de densidad y los diagnósticos posteriores de MCMC mostraron una adecuada convergencia (Rhat<1.1) y un tamaño de muestra efectivo (>10000 en la mayoría de los parámetros). Se aplicaron priors débilmente informativos (dirichlet(1) para los parámetros simplex ζ, t student(3, 0, 2.5) para las intercepciones, y priors planos para el resto. El tamaño de muestra límite soporta un modelo de 30-45 coeficientes.

Se utilizaron modelos similares para la calidad de vida, la depresión y la ansiedad. Todos los modelos se emplearon para calcular las reducciones absolutas del riesgo (ARR) para cada objetivo (ajustadas al promedio de las variables continuas o al nivel más frecuente de las discretas). También se reportó el inverso del ARR, interpretado como el número necesario a exponer (NNE) a un factor de riesgo para obtener un caso adicional de resultado negativo, bajo la asunción de que los objetivos son independientes. Otros análisis exploratorios aplicaron correlaciones de rango de Tau de Kendall, o pruebas de $\chi 2$ para proporciones.

5.5.4 Artículo 4

Se aplicaron estadísticas descriptivas para datos demográficos y respuestas a las encuestas. Se utilizaron frecuencias absolutas para datos categóricos mientras que los datos cuantitativos se expresaron mediante la media y la desviación estándar.

Se realizaron análisis descriptivos adicionales agrupando a los pacientes según el tipo de cáncer. Realizamos pruebas de chi-cuadrado y t bivariadas para evaluar las diferencias entre los pacientes con cáncer localizado y avanzado en términos de características sociodemográficas y clínicas. Se utilizaron análisis ANOVA para investigar las diferencias en las características psicológicas asociadas con el

estado del grupo (cáncer avanzado o localizado) y representadas por EORTC-QLQ-C30, SWLS y BSI. Además, se empleó el coeficiente eta cuadrada (η2) para estimar el tamaño del efecto en las variables continuas, oscilando su valor entre 0 y 1. Un valor con η2 ~ 0,01 indica un tamaño del efecto pequeño, η2 ~ 0,06 denota un tamaño de efecto mediano y η2 >0,14 indica un tamaño de efecto grande.

Por último, se realizó un análisis MANCOVA para examinar el efecto de los niveles pretest y el estado de los grupos (cáncer avanzado y localizado) sobre las características psicológicas (EORTC-QLQ-C30, SWLS y BSI), ajustando por variables como la edad, el sito del tumor y el estado general ECOG.

5.5.5 Artículo 5

El cuestionario BSI-18 se utilizó como referencia para comparar con el EF-EORTC-QLQ-C30. El BSI-18 aplica la regla del caso clínico, desarrollada originalmente para el SCL-90, para identificar a las personas con angustia psicológica significativa, marcada por un *T-cut-off* de 63 o superior.

De acuerdo con nuestra referencia, la angustia psicológica identificada por el EF-EORTC-QLQ-C30 se definió como verdadero positivo (caso correctamente identificado), verdadero negativo (no caso correctamente identificado), falso positivo (caso incorrectamente identificado) y falso negativo (no caso incorrectamente identificado).

Se calcularon cinco métricas claves: (1) el número total de pacientes correctamente identificados con angustia psicológica, precisión general de la prueba calculada como [TP + TN]/[TP + TN + FP + FN]; (2) la proporción de positivos identificados correctamente, tasa de verdaderos positivos/sensibilidad calculada como TP/[TP + FN]); (3) la proporción de negativos correctamente identificados, negativo verdadero/ especificidad calculada como TN/[TN + FP]); (4) el valor predictivo positivo calculado como TP/[TP + FP]), y (5) el valor predictivo negativo calculado como TN/[TN + FN]).

Además, se evaluó la capacidad discriminatoria de la puntuación EF-EORTC-QLQ30 utilizando el área bajo la curva característica operativa del receptor (ROC) (AUC). Esta medida resumió la habilidad del EF-EORTC-QLQ-C30 para discriminar entre pacientes con y sin angustia psicológica. Una AUC más alta fue indicativa de una mejor capacidad discriminatoria. Utilizamos un umbral AUC ≥ 0,70 para el EF-EORTC-QLQ-C30, el mismo estándar que aplicamos en nuestro análisis anterior.

6. RESULTADOS

6.1 Artículo 1

6.1.1 Descripción de la población

La muestra para este **primer artículo** estuvo compuesta por 508 pacientes, de los cuales 273 (53,7%) eran hombres y la edad media se situó en 54,9 años (desviación estándar=10,1). La mayor parte estaban casados o en una relación de pareja (83,1%) y tenían hijos (83,7%). El 47,8% tenían un nivel de educación primaria.

Los cánceres más comunes fueron los del tracto digestivos (40,6%) broncopulmonares (29,1%), y de mama (8,5%). La histología de adenocarcinoma fue la más común (63%) y la mayor parte de las neoplasias se encontraban en estadio IV (79,7%), el resto eran estadios III irresecables. El tratamiento más frecuentemente administrado fue quimioterapia (55,7%), quimioterapia con un agente biológico (10,6%) o con inmunoterapia (9,6%).

La supervivencia estimada fue menor a 18 meses en el 48,8% de la muestra (**Tabla 1.1**)

Tabla 1.1 Características basales (n=508)

Variables	**N**	**%**
Sexo		
Mujer	235	46.3
Hombre	273	53.7
Edad (años)		
<45	17	3.4
45-70	239	47.0
>70	252	49.6
Estado general ECOG		
0	174	34.3
1	300	59.1
2	31	6.1
3	3	0.6
Comorbilidades		
Enfermedad cardiovascular	206	40.6
Enfermedad crónica	11	2.2
Enfermedad psiquiátrica	21	4.1
Cardiovascular + enfermedad crónica	34	6.7

Cardiovascular + enfermedad crónica + enfermedad psiquiátrica	17	3.3
Obesidad (índice de masas corporal ≥30)	80	15.7
Pérdida de peso	69	13.6
Otras comorbilidades	70	13.8
Estado civil		
Casado o con pareja	335	83.1
Soltero/divorciado/viudo	68	16.9
Nivel educacional		
Estudios primaros	243	47.8
Estudios secundarios o superior	265	52.2
Hijos		
Con hijos	425	83.7
Sin hijos	83	16.3
Localización tumoral		
Broncopulmonar	148	29.1
Digestivo *Colorrectal* *No colorrectal*	206 103 101	40.6
Ginecológico y mama *Mama* *Ginecológico*	43 32 11	8.5
Otros	111	21.9
Histología		
Adenocarcinoma	320	63.0
Otros	188	37.0
Estadio		
Localmente avanzado	103	20.3
IV (Metastásico)	405	79.7
Uso de biomarcador para decisión terapéutica		
No	375	73.8
Si	133	26.2
Supervivencia estimada		
<18 meses	248	48.8
≥18 meses	260	51.2
Tipo de tratamiento		
Quimioterapia	283	55.7
Quimioterapia e inmunoterapia	49	9.6
Quimioterapia y terapia dirigida	54	10.6
Inmunoterapia	35	6.9
Terapia dirigida a	28	5.5
Otras	58	11.4

6.1.2 Prevalencia de fatiga y angustia emocional

De la totalidad de la muestra, 283 pacientes (55,7%) manifestaron padecer fatiga, con una puntuación ≥ 39, conforme a los criterios establecidos por Giesinger et al. [29]. Las mujeres presentaron más fatiga que los hombres ($\chi 2$= 11.689; p< 0.001), mientras que no se encontraron diferencias significativas en la incidencia de fatiga entre distintos estadios de la enfermedad o en relación con las comorbilidades.

Por otro lado, la angustia emocional estuvo presente en el 47,7% de los pacientes, correspondiendo a aquellos con una puntuación T ≥ 67. Al igual que en el caso de la fatiga, las mujeres presentaron mayor angustia emocional que los hombres ($\chi 2$= 6.347; p= 0.012). Sin embargo, no se encontraron diferencias significativas según el estadio o las comorbilidades existentes (p= 0.456) **(Tabla 1.2).**

Tabla 1.2 Fatiga, malestar emocional e incertidumbre en función de sexo y estadio

Variables	**Fatiga**		**Malestar emocional**		**Incertidumbre**	
Sexo (n, %)	**No (FA <38.9)**	**Fatiga (FA ≥39)**	**No (ED <66.9)**	**Malestar Em (ED ≥67)**	**No (UN <15.9)**	**Fatiga (UN ≥16)**
Hombre	140 (62.2)	133 (47.0)	155 (58.7)	113 (47.5)	172 (53.3)	101 (37.0)
Mujer	85 (37.8)	150 (53.0)	109 (41.3)	125 (52.5)	151 (46.7)	84 (45.4)
p	<0.001*		0.012*		0.770	
Estadio (n, %)						
Localmente avanzado	40 (17.8)	63 (22.3)	57 (21.6)	45 (18.9)	61 (18.9)	42 (22.7)
Metastásico	185 (82.2)	220 (77.7)	207 (78.4)	193 (81.1)	262 (81.1)	143 (77.3)
p	0.212		0.577		0.303	
Comorbilidades (n, %)						
Cardiovascular	112 (49.8)	142 (50.2)	131 (49.6)	119 (50.0)	176 (54.5)	78 (42.2)
Otras	113 (50.2)	141 (49.8)	133 (50.4)	116 (50.0)	147 (45.5)	107 (57.8)
p	0.929		0.932		.007**	
ECOG (n, %)						
0	104 (46.2)	70 (24.7)	101 (38.3)	70 (29.4)	121 (37.5)	53 (28.6)
1	113 (50.2)	187 (66.1)	151 (57.2)	147 (61.8)	187 (57.9)	113 (61.1)
2	7 (3.1)	24 (8.5)	10 (3.8)	20 (8.4)	13 (4.0)	18 (9.7)
3	1 (0.4)	2 (0.7)	2 (0.8)	1 (0.4)	2 (0.6)	1 (0.5)
p	0.001*		0.046*		.027*	

*Estos valores indican una significancia del 5%

6.1.3 Relación de la fatiga, la angustia emocional y la incertidumbre sobre la enfermedad con la calidad de vida

En un primer análisis de correlaciones bivariadas, la fatiga, la angustia emocional, la incertidumbre de la enfermedad y el estado general ECOG se asociaron significativamente con la calidad de vida (con correlaciones que variaban de -0.23 a -0.71, todas con p< 0.001) **(Tabla 1.3).** En un análisis de regresión lineal donde se incorporaron la fatiga, la angustia emocional, la incertidumbre sobre la enfermedad y el ECOG como variables predictoras, y se consideraron las variables demográficas edad, sexo y comorbilidades, reveló una influencia significativa de la fatiga, la angustia emocional, la incertidumbre respecto a la enfermedad y el estado general ECOG sobre la calidad de vida (F= 129,50, p<0,001). Este modelo mostró un alto grado de capacidad explicativa (R2 ajustado = 0.61 para el modelo), siguiendo las directrices de Cohen (f2 = 1.60) [104]. La presencia de más síntomas medidos por estas escalas se asoció con una peor calidad de vida **(Tabla 1.4)**.

Tabla 1.3 Correlación de fatiga, malestar emocional e incertidumbre sobre la enfermedad con calidad de vida

Variables	Fatiga	Malestar emocional	Incertidumbre sobre la enfermedad	ECOG	Calidad de vida
Fatiga	1				
Malestar emocional	0.559**	1			
Incertidumbre sobre la enfermedad	0.177**	0.264**	1		
ECOG	0.237**	0.129**	0.105*		
Calidad de vida	-0.705**	-0.645**	-0.298**	-0.251**	1
**p<.001; * p<.005					

Tabla 1.4 Modelo de regresión lineal como predictor de calidad de vida

	Calidad de vida				
Predictor	**Estimación**	**R^2**	**t**	**P**	**Cl**
(Intercept)	116.682		17.852	0.001*	103.8-129.5
Fatiga	-0.275	0.49	-13.551	0.001*	-0.31- -0.23
Malestar emocional	-0.869	0.59	-9.862	0.001*	-1.0- -0.69
Incertidumbre sobre la enfermedad	-0.546	0.60	-3.896	0.001*	-0.82- -0.27
ECOG	-2.556	0.61	-2.711	0.001*	-4.4--0.70
Sexo: Hombre	-0.390		-0.360	0.719	-0.13- 0.07
Edad	-.027		-0.493	0.622	-2.50- 1.40
R^2 ajustado total		0.61			

*Estos valores indican una significancia del 5%

6.2 Artículo 2

6.2.1 Características demográficas y clínicas de la población

Para el análisis del **segundo artículo,** se incluyeron datos de 837 sujetos (edad media, 65 años ± 10,6) de los que se excluyeron los que no cumplían criterios de inclusión (n = 10).

La mayoría de los participantes eran hombres (54%); el 78% estaban casados; el 52% completó la escuela secundaria; y el 51% estaban jubilados o desempleados. Los tumores más comunes fueron broncopulmonares (32%), colorrectales (15%), pancreáticos (10%), mamarios (7%) y gástricos (6%). La histología tipo adenocarcinoma fue la más prevalente (63%) y la mayoría de los diagnósticos de cáncer correspondieron al estadio IV (81%). El tratamiento más habitual fue la quimioterapia como monoterapia o combinada con otras modalidades de tratamiento (80%). La supervivencia estimada fue inferior a 12 meses para el 27% de la muestra.

Según los puntos de corte establecidos, la prevalencia general de síntomas depresivos en la población estudiada fue del 46 %. Los valores medios para los síntomas depresivos fueron 63,4 ± 7,1. El ANOVA unidireccional reveló

relaciones estadísticamente significativas entre los síntomas depresivos y el sexo (F= 17,685, p= 0,001, eta cuadrado parcial = 0,021), la edad (F= 2,691, p= 0,030, eta cuadrado parcial = 0,013), el estado civil (F = 7,881, p = 0,005, eta cuadrado parcial = 0,012) y la presencia de cáncer recurrente (F = 6,540, p = 0,011, eta cuadrado parcial = 0,008); no se encontraron diferencias significativas para el resto de las variables **(Tabla 2.1).** Utilizando un punto de corte < 75 [105] para identificar a las personas con problemas funcionales, el 41% de los participantes indicó que tenía dificultades para realizar las actividades cotidianas**.**

Tabla 2.1 Características basales (n=837)

Variables		**n (%)**
Edad (M; SD)	65.2 ±10.6	
Sexo	Hombre	454 (54)
	Mujer	383 (46)
Estado civil	Casado o con pareja de hecho	653 (78)
	Soltero	174 (22)
Nivel educacional	≤ Primaria	405 (48)
	≥ Secundaria	432 (52)
Empleo	Desempleado	422 (51)
	Empleado	415 (49)
Localización de tumor primario	Broncopulmonar	266 (32)
	Colon	122 (15)
	Páncreas	83 (10)
	Mama	62 (7)
	Estómago	47 (6)
	Otros	257 (31)
Histología	Adenocarcinoma	526 (63)
	Otros	311 (37)
Cáncer recurrente	Si	677 (19)
	No	160 (81)
Estadio	Localmente avanzado	161 (19)
	IV	676 (81)
Tratamiento oncológico	Quimioterapia	670 (80)
	Otros	167 (20)
Supervivencia estimada	<12 meses	224 (27)
	>12.1 meses	613 (73)
Abreviaciones: M, Media; SD, desviación estándar		

6.2.2 Correlaciones entre variables

Los síntomas depresivos se correlacionaron positivamente con el sexo (r = 0,144, p < 0,001), el estado civil (r = 0,108, p = 0,005), la puntuación de la escala de síntomas (r = 0,476, p < 0,001) y la actitud negativa (r = 0,534, p< 0,001), mientras que se correlacionaron negativamente con la edad (r = −0,081, p= 0,020), la escala funcional (r = −0,618, p< 0,001) y la actitud positiva (r = −0,298, p< 0,001). No se detectaron correlaciones significativas entre la evitación cognitiva y los síntomas depresivos (**Tabla 2.2**).

Tabla 2.2 Correlación entre síntomas depresivos y variables a estudio.

Variables	1	Edad	Sexo	Estado Civil	5	6	7	8	9
1.Depresión	1								
2. Edad	-0.081*	1							
3. Sexo	0.144**	-0.068*	1						
4. Estado civil	0.108**	-0.182**	0.126**	1					
5. Escala de síntomas	0.476**	-0.104**	0.139**	0.127**	1				
6. Escala funcional	-0.618**	0.063	-0.179**	-0.090*	-0.764**	1	-0.419**		
7. Emoción negativa	0.534**	0.071*	0.051	0.037	0.298**	-0.419**	1		
8. Emoción positiva	-0.298**	-0.100**	-0.093**	0.014	-0.116**	0.215**	-0.174**	1	
9. Evitación cognitiva	0.064	-0.048	-0.039	0.036	0.052	-0.043	0.277**	0.447**	1

*p<0.05; **p<0.01. Edad como variable continua; Sexo: 0=Hombre, 1=Mujer; Estado civil: 0=Casado o con pareja de hecho, 1=Soltero/viudo/divorciado

6.2.3 Relación entre puntuaciones de escala funcional y de síntomas, estrategias de afrontamiento y depresión: análisis de trayectorias

El modelo exhibió un excelente ajuste con los datos ($\chi 2$= 14,718; p= 0,005; CFI = 0,993; NFI= 0,990; TLI= 0,982; RMSEA= 0,057 (IC del 90% = [0,028, 0,089]). Como se muestra en la **Figura 2.1**, los síntomas se vincularon de forma directa y negativa con la puntuación de la escala funcional (β = −0,76, p< 0,01); la

puntuación de la escala funcional se asoció de manera directa y positiva con la actitud positiva (β= 0,22, p< 0,01) y de forma negativa con la actitud negativa (β= -0,42, p< 0,01) y la depresión (β= -0,46, p< 0,01). La actitud negativa se asoció positivamente con la depresión (β= 0,32, p< 0,01) y la actitud positiva se asoció negativamente con la depresión (β= - 0,15, p< 0,01); cuantos más síntomas presentaban los pacientes, peor era su estado funcional y más aumentaban los síntomas depresivos; además, la actitud positiva y la actitud negativa mediaron en la asociación entre el estado funcional y los síntomas depresivos. (**Figura 2.1**).

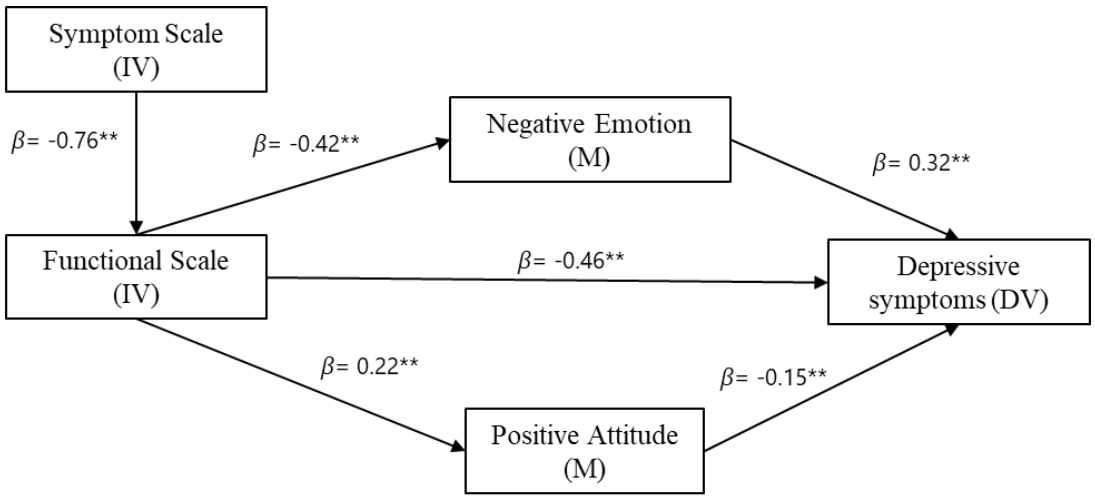

Figura 2.1 Modelo predictive de síntomas depresivos en pacientes con cáncer avanzado.

Cuantos más síntomas presentaban los pacientes, peor era su estado funcional y más aumentaban los síntomas depresivos. Las estrategias de afrontamiento pueden ayudar a mediar en esta relación. Los sujetos que presentaban un peor estado funcional y percibían la enfermedad como una fuente de estrés inmanejable, con presencia de sentimientos de desesperanza, preocupación ansiosa, angustia y desánimo (actitud negativa) experimentaban cada cambio como una señal de que su situación se estaba deteriorando, lo que resultaba en

un incremento de la percepción de malestar y en la aparición de más síntomas depresivos.

En cambio, aquellos que tenían un estilo de afrontamiento más activo y positivo, que intentaban gestionar su situación buscando alternativas y soluciones, y mantenían sus expectativas y confianza en poder adaptarse a los retos de la enfermedad (actitud positiva), presentaban menos síntomas de depresión.

6.3 Artículo 3

6.3.1 Pacientes

Para el **tercer artículo** se analizó una base de datos que contenía 550 pacientes con cáncer avanzado irresecable (incurable) reclutados durante dos años (2020 y 2021). Las características basales se detallan en la **Tabla 3.1**. La mayoría eran varones (58%, n=319) con una mediana de edad de 66 años (rango, 18-90). El 24% (n=133) tenía más de 70 años. Los tumores más frecuentes fueron el broncopulmonar (37%, n=203), el colorrectal (22%, n=123), y el digestivo no colorrectal (22%, n=122). Con respecto a terapias, el 21% (n=117) recibió inmunoterapia, y el 23% (n=126) terapias dirigidas con o sin quimioterapia.

Los pacientes presentaron una gran preocupación por su salud, el 51% (n=282) tenía miedo a la muerte, y el 84% declaró conocer la gravedad de su enfermedad. Sin embargo, la mayoría (74%, 407/500) estuvo de acuerdo en que el tratamiento ayudaría a curar el cáncer. El 68% (378/550) aceptó la administración de terapias de baja eficacia, y la mayoría (>90%) se mostraron partidarios de recibir tratamientos para mejorar la respuesta tumoral o la calidad de vida (**Anexo 5**).

En contraposición, la supervivencia estimada por el oncólogo fue de 22.6 meses (rango 5-100), y sólo el 13.4% (n=74) de los médicos estaba de acuerdo o muy de acuerdo en la existencia de opciones de supervivencia a largo plazo. Según los oncólogos, tanto la ocultación de información al paciente (2%, n=10) como la

divulgación de datos precisos de supervivencia (2%, n=12) fueron infrecuentes. El estilo más común de información fue el cualitativo sin alusión directa a la muerte (65%, n=356). De los que informaron de forma cuantitativa, el 38% (24/63) usó datos relativos, el 49% (31/63) resultados absolutos, el 6% (4/63) mostró el ensayo pivotal, y no estuvo claro en el resto. La relación entre el tipo de divulgación de información y las expectativas se muestra en el **Anexo 5**.

Con respecto a preferencias de control, sólo el 20% (n=105) deseaba que las decisiones fueran tomadas por el médico de manera independiente. Los niveles de satisfacción con la entrevista, y con la relación médico-paciente fueron elevados.

Tabla 3.1 Características basales (n=550)

	N (%)
Edad, mediana (rango)	66 (18-90)
Sexo, femenino	231 (42%)
Tumor	
Colorrectal	123 (22.3)
Pulmón	203 (36.9)
Cabeza y cuello	16 (2.9)
Gastrointestinal superior	122 (22.1)
Mama	29 (5.2)
Otros	57 (10.3)
ECOG PS	
0	189 (34.3)
1	325 (59.0)
≥2	36 (6.5)
Perspectiva oncológica	
Metástasis irresecables	401 (72.9)
Metástasis potencialmente resecables	41 (7.4)
Metástasis resecables	8 (1.4)
Localmente avanzado irresecable	89 (16.1)
Localmente avanzado potencialmente resecable	11 (2.0)
Terapia	
Inmunoterapia	117 (21.1)
Quimioterapia	306 (55.6)
Terapia antidiana	126 (22.9)
QLQ-C30 Escala de síntomas, mediana (rango)	27.1 (0-94.4)
Perfil de información administrada	
No informado debido a la conspiración	3 (0.55)
No reportado como inapropiado	7 (1.27)

Información cualitativa sin aludir a la muerte	356 (64.7)
Información cualitativa alusiva a la muerte	121 (22.0)
Información cuantitativa aproximada	51 (9.2)
Información cuantitativa precisa	12 (2.1)
Estado civil	
Casados o en pareja	374 (68.0)
Soltero	62 (11.2)
Divorciado	63 (11.4)
Viudo	51 (9.2)
Número de niños	
0	83 (15.0)
1	104 (18.9)
2	227 (41.2)
≥3	136 (24.7)
Nivel educativo	
Sin educación	49 (8.9)
Enseñanza primaria	217 (39.4)
Enseñanza secundaria	153 (27.8)
Estudios universitarios	131 (23.8)
Situación laboral	
Desempleado	2 (0.3)
Jubilado	248 (45.0)
Trabajador a tiempo parcial	1 (0.1)
Trabajador a tiempo completo	299 (54.3)
Cuidador principal	
Solo, sin soporte	39 (7.0)
Familia	498 (90.5)
Amigo/conocido	9 (1.6)
Personal de una institución (residencia)	4 (0.7)

6.3.2 Predictores de conocimiento pronóstico impreciso

El modelo ordinal, índico que la espiritualidad, el apoyo social percibido, la expectativa de vida prolongada y la ausencia de síntomas aumentaron la creencia en la curabilidad (**Anexo 6**). En cambio, una comprensión precisa del pronóstico fue más frecuente en mujeres con cáncer de mama, sujetos con miedo a la muerte, o en aquellos a quienes se les proporcionó información completa. No hubo indicios de no-linealidad en el efecto de la edad. La Figura del **Anexo 7** muestra los efectos condicionales ajustados por los valores fijos de las covariables, ilustrando la alta probabilidad de una conciencia pronóstica inexacta en varios perfiles (probabilidad de creencia en la curabilidad en el 80-90% de los sujetos en diversos escenarios).

6.3.3 Predictores del interés potencial en terapias de baja eficacia

La regresión ordinal para predecir el interés en terapias de baja eficacia se muestra en la tabla del **Anexo 8**. La creencia en la curabilidad del cáncer, la esperanza y el apoyo social percibido se asociaron con un mayor interés (**Anexo 9**). La asociación con la edad fue no-lineal, con edades extremas (jóvenes y mayores) relacionadas con mayor aceptación. Otros factores asociados con mayor interés en terapias de baja eficacia (probabilidad posterior de direccionalidad >85%) fueron la preocupación por la muerte, el sexo femenino, y tener un estado general ECOG 0-1. La divulgación del pronóstico se asoció con una probabilidad posterior del 86%.

El interés por terapias de baja eficacia en sujetos con máxima o nula consciencia pronóstica fue del 78.8% (IC 95%, 75.4-82.2) frente al 63.3% (IC 95%, 59.3-67.4), respectivamente. El número de individuos expuestos a un máximo conocimiento pronóstico inexacto necesario para que un individuo extra optara por una terapia de baja eficacia (NNE) fue de 6.4 (IC 95%, 3.6-29.3). La probabilidad de aceptación de terapias de baja eficacia varió entre el 82.9% y 71.2% en sujetos informados cuantitativamente de manera precisa o no informados por colusión (el NNE no se estimó porque el IC 95% de la ARR incluye el 0).

6.3.4 Impacto de la divulgación de información/ Divulgación pronóstica sobre otros resultados

La creencia en la posibilidad de curación se correlacionó con varios resultados, incluyendo un mayor espíritu de lucha, fatalismo/aceptación estoica, esperanza, salud global, satisfacción con las decisiones tomadas y la atención recibida (**Anexo 10**). Por otro lado, la creencia en la curabilidad se correlacionó de forma negativa con la incertidumbre, impotencia/desesperanza, depresión, ansiedad, somatización, y diversos síntomas.

Las predicciones ajustadas para la depresión variaron del 86.6% (IC 95%, 83.7-89.4) al 68.0% (IC 95%, 64.1-71.1), en sujetos con mínima y máxima consciencia pronóstica imprecisa, respectivamente. Para el caso de la ansiedad, las predicciones ajustadas fueron del 86.1 (IC 95%, 83.8-89.6) y el 71.8% (IC 95%, 68.0-75.5), respectivamente. Con respecto a la baja calidad de vida, las predicciones ajustadas para pacientes con máxima o ninguna consciencia pronóstica fueron del 82.6% (IC 95%, 79.4-85.7) y el 69.6% (IC 95%, 65.7.2-73.4), respectivamente. El número necesario de sujetos expuestos a un conocimiento exacto del pronóstico para obtener un caso extra de depresión, ansiedad o calidad de vida pobre (NNE ajustado) fue de 5.3 (IC 95%, 3.5-10.6), 8.6 (4.6-56.7), y 7.6 (4.3-35.7), respectivamente.

6.4 Artículo 4

6.4.1 Características basales de la muestra

Para el **cuarto artículo** se examinaron 1.893 pacientes. De estos, 1807 fueron elegibles para este análisis y 96 fueron descartados (30 no cumplieron con los criterios de inclusión, 45 cumplieron algún criterio de exclusión y 21 tenían datos incompletos en el momento del análisis).

Novecientos cuarenta y cuatro (52%) pacientes tenían un cáncer localizado resecado y 863 tenían un cáncer avanzado irresecable. Las características sociodemográficas y clínicas basales se presentan en la **Tabla 4.1**. La mediana de edad de los pacientes con enfermedad localizada y avanzada fue de 59.0 y 65 años, respectivamente. Los hombres presentaron con más frecuencia que las mujeres cáncer avanzado. La proporción de pacientes que no trabajaban era mayor en el grupo de enfermedad avanzada, la mayor parte de ellos estaban jubilados, mientras que en la cohorte de pacientes con enfermedad localizada la mayor parte de los que no trabajaban estaban desempleados o de baja laboral. Los tumores más comunes fueron colorrectales (43%) y mama (38%) en pacientes

con cáncer localizado y broncopulmonar (32%), digestivo no colorrectal (23%) y colorrectal (15%) en pacientes con cáncer avanzado. En sujetos con enfermedad localizada, el tratamiento consistió en cirugía y quimioterapia adyuvante, 67% solo quimioterapia y 33% quimioterapia asociada con radioterapia. Los pacientes que presentaban enfermedad avanzada recibieron mayor variedad de tratamientos sistémicos: quimioterapia en monoterapia (53%), inmunoterapia +- quimioterapia (7%) y agente biológico +- quimioterapia (5%). Un 8% de los pacientes con enfermedad avanzada fallecieron durante los 3 meses de seguimiento del estudio (n=71) frente a un 2% de fallecimientos durante los 6 meses de seguimiento en aquellos que presentaban enfermedad localizada (n=22).

Tabla 4.1 Características demográficas y clínicas de los pacientes (n=1807)

Características demográficas y clínicas	TOTAL (n=1807)	Cáncer localizado (n=944)	Cáncer avanzado (n= 863)	t/χ2	p
Sexo: n (%)					
Hombres	843 (47)	370 (39)	473 (55)	44.163	0.001
Mujeres	964 (53)	574 (61)	390 (45)		
Edad (años): media (DE)	60 (11)	59 (12)	65 (11)	-11.825	0.001
Estado civil					
Casado/en pareja: n (%)	1301 (72)	719 (76)	582 (67)	17.028	0.001
Nivel educativo: n (%)					
Básico	919 (51)	509 (54)	410 (48)	7.414	0.006
Intermedio	888 (49)	435 (46)	453 (52)		
Desempleado: n (%)	849 (47)	393 (42)	456 (53)	22.735	0.001
Cancer: n (%)					
Broncopulmonar	320 (18)	43 (5)	277 (32)	543.32	0.001
Colorrectal	534 (30)	403 (43)	131 (15)		
Digestivo no colorrectal	268 (15)	69 (7)	199 (23)		
Mama	458 (25)	357 (38)	101 (12)		
Tipo de tratamiento sistémico					
Quimioterapia (CT)	1124 (60)	669 (67)	455 (53)	777.53	0.001
CT y radioterapia	335 (18)	335 (33)	0 (0)		
Inmunoterapia con/sin CT	62 (3)	0 (0)	62 (7)		
Terapia dirigida con/sin CT	46 (3)	0 (0)	46 (5)		
Otros	300 (16)	0 (0)	300 (35)		
Muerte n (%)	93 (5%)	22 (2)	71 (8)	36.205	0.001
Abreviaturas: n = número, DE = desviación estándar.					

6.4.2 Comparación de calidad de vida y satisfacción con la vida

En relación con la escala EORTC-QLQ-C30, los pacientes con enfermedad avanzada antes de iniciar el tratamiento antineoplásico sistémico mostraron peores puntaciones en limitaciones físicas, de rol, emocionales, cognitivas y sociales en comparación con los pacientes con enfermedad localizada antes de iniciar tratamiento antineoplásico complementario a la cirugía (todos $p < 0,001$). Asimismo, los pacientes con enfermedad avanzada presentaron más síntomas en todas las escalas de síntomas (fatiga, náuseas, dolor, disnea, insomnio, pérdida de apetito y diarrea (todos $p<.001$). No hubo diferencias en la escala de dificultades financieras. Al inicio del tratamiento se reportaron más limitaciones funcionales, más síntomas y peor estado de salud (todos $p<0.001$), entre los pacientes con cáncer avanzado.

Los pacientes con cáncer localizado reportaron más satisfacción con su vida y presentaban menos malestar psicológico que aquellos con un cáncer avanzado ($p<0.001$) (T**abla 4.2).**

Tabla 4.2 Cómo la extensión del cáncer afecta la calidad de vida, el bienestar psicológico y la satisfacción con la vida

	TOTAL (n=1807)	Cáncer localizado (n=944)	Cáncer avanzado (n= 863)	F	p	Eta squared
Calidad de vida (EORTC QoL-QLQ-C30)[a]						
Función física	79.1 (22.9)	85.9 (15.6)	71.6 (26.9)	193.689	0.001	0.097
Función de rol	72.5 (30.6)	76.3 (26.3)	68.4 (34.2)	30.449	0.001	0.017
Función emocional	67.9 (27.4)	72.1 (24.9)	63.4 (29.4)	45.271	0.001	0.025
Función cognitiva	81.9 (23.7)	85.6 (20.7)	78.0 (26.0)	47.512	0.001	0.026
Función social	72.6 (30.2)	77.1 (25.4)	67.8 (34.1)	43.011	0.001	0.023
Fatiga	36.9 (29.1)	29.1 (24.3)	45.4 (31.5)	150.468	0.001	0.077
Náuseas/emesis	12.6 (23.9)	8.9 (18.3)	16.5 (28.2)	46.508	0.001	0.025
Dolor	26.2 (30.3)	17.9 (23.2)	35.2 (34.2)	158.575	0.001	0.081
Disnea	8.9 (22.6)	4.9 (15.8)	13.3 (27.5)	63.922	0.001	0.034
Insomnio	37.4 (35.6)	31.2 (32.2)	44.2 (37.9)	61.818	0.001	0.033
Pérdida de apetito	26.8 (34.9)	20.1 (29.5)	34.1 (38.7)	76.059	0.001	0.041
Estreñimiento	27.8 (35.5)	20.9 (30.1)	35.2 (39.2)	75.757	0.001	0.041
Diarrea	16.7 (29.2)	13.6 (24.3)	20.2 (33.3)	23.365	0.001	0.013
Dificultades financieras	16.7 (30.1)	15.6 (28.6)	18.0 (31.7)	2.647	0.104	0.001
Escala FUNCTIONAL	74.7 (20.7)	79.3 (17.1)	69.8 (23.1)	97.417	0.001	0.052
Escala de SINTOMAS	23.4 (18.4)	18.1 (14.9)	29.2 (20.1)	174.748	0.001	0.089
Escala de estado de SALUD	65.3 (23.1)	70.2 (20.2)	60.1 (24.8)	90.517	0.001	0.048
Satisfacción vital (SWLS)[b]	26.4 (6.3)	27.0 (5.8)	25.7 (6.7)	19.096	0.001	0.011
Malestar psicológico (BSI)	65.3 (7.4)	63.7 (7.1)	67.1 (7.4)	97.968	0.001	0.052

Abreviaturas: EORTC-QoL-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, SWLS= Satisfaction with life scale. [a] Escala de 0 a 100. [b] Escala de 5 a 35 para la satisfacción con la vida. Los valores en negrita indican significación en el nivel del 5%.

6.4.3 Cambios psicológicos y somáticos tras el tratamiento oncológico

Se recogieron los cuestionarios de seguimiento en 624 pacientes con cáncer localizado y en 330 con cáncer avanzado para examinar el cambio producido por el efecto del tratamiento sistémico antineoplásico. Estas evaluaciones incluyeron la escala EORTC-QLQ-C30 antes y después del tratamiento oncológico, tras unos 3 meses (pacientes con enfermedad avanzada) y tras unos 6 meses o fin de quimioterapia adyuvante (pacientes con enfermedad localizada) (**Tabla 4.3**). Dentro del grupo de pacientes con cáncer resecado se registraron 22 muertes, 88

pacientes abandonaron la quimioterapia antes de acabar el tratamiento adyuvante, probablemente por la toxicidad asociada (aunque esto no fue evaluado), y en 210 no se pudo obtener el cuestionario final. En el grupo de pacientes con cáncer avanzado se contabilizaron 71 muertes y 462 pérdidas de seguimiento, 365 de las cuales se debieron a abandono precoz del tratamiento por progresión o deterioro clínico.

Ajustando por edad, tipo de tumor primario y estado general ECOG, se observó un empeoramiento en las escalas funcional, de rol emocional, cognitiva y social para los pacientes con enfermedad localizada, así como un aumento de todos los síntomas. En los pacientes con enfermedad avanzada se percibió una disminución menos severa que en la otra población. Al comparar ambos grupos, se identificó una diferencia significativa independientemente del ECOG, la edad o el origen tumoral, con un mayor detrimento de la calidad de vida en todos los aspectos en los pacientes con enfermedad resecada (salvo en la escala de dificultades económicas).

Tabla 4.3 Análisis de la varianza de las mediciones repetidas antes y después del tratamiento sistémico ajustadas por edad, sitio del tumor y estado funcional ECOG (n = 954)

Escalas	Cáncer localizado (n=624)		Cáncer avanzado (n=330)		MANCOVA Resultados, F		
	Pre Media (DE)	Post Media (DE)	Pre Media (DE)	Post Media (DE)	Tiempo* tumor	Tiempo	Tumor
Malestar psicológico (BSI)	66.9 (7.4)	67.0 (7.4)	64.5 (7.1)	65.5 (6.9)	19.161	.415	22.595
Calidad de vida (EORTC-QLQ-C30)							
Función física	86.2 (15.1)	72.3 (26.3)	83.6 (17.9)	74.9 (24.2)	2.913	.001	63.297
Función de rol	76.5 (25.9)	70.4 (33.1)	75.8 (27.4)	73.2 (30.9)	.343	1.329	6.558
Función emocional	72.3 (24.6)	65.4 (29.8)	76.0 (25.2)	72.5 (27.2)	3.939	6.533	10.201
Función cognitiva	85.9 (20.3)	79.8 (23.9)	82.7 (23.1)	79.7 (24.4)	.959	.416	8.895
Función social	77.7 (25.1)	69.2 (32.2)	76.7 (27.0)	72.1 (31.4)	1.341	1.325	21.666
Fatiga	28.3 (23.8)	44.6 (31.0)	35.7 (27.5)	38.9 (30.2)	16.909	.767	31.008
Náuseas/emesis	8.8 (17.0)	17.0 (28.9)	10.9 (20.1)	13.8 (24.8)	8.681	2.648	11.428
Dolor	17.1 (23.1)	34.8 (34.0)	20.0 (26.3)	24.5 (29.4)	21.285	3.011	45.526
Disnea	4.5 (14.9)	11.8 (25.2)	6.6 (19.0)	10.2 (23.1)	1.807	.846	19.828
Insomnio	30.7 (31.9)	42.0 (38.1)	32.1 (33.3)	31.9 (35.4)	14.433	9.704	6.437
Pérdida apetito	16.5 (29.2)	34.1 (39.6)	20.4 (30.2)	27.3 (33.6)	2.819	.070	11.408
Estrelimiento	20.8 (29.9)	35.0 (38.9)	22.9 (31.3)	29.1 (34.3)	6.374	.965	22.569
Diarrea	12.7 (22.5)	19.6 (33.3)	15.7 (26.5)	22.4 (32.9)	.275	.974	15.395
Financiero	15.2 (27.7)	17.2 (31.6)	13.7 (27.4)	15.7 (29.8)	.669	7.175	2.545
Es.FUNCTIONAL	79.7 (16.8)	71.4 (21.9)	79.0 (19.5)	74.5 (22.1)	2.625	1.451	27.281
Es. SINTOMAS	17.5 (14.1)	28.5 (20.2)	19.8 (17.2)	23.8 (18.4)	18.229	6.238	42.266
Es. SALUD	71.1 (19.7)	60.7 (25.3)	68.7 (23.6)	59.3 (26.6)	.052	.432	38.249

Abreviaturas: EORTC-QoL-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, SWLS= Satisfaction with life scale. [a] Escala de 0 a 100. [b] Escala de 5 a 35 para la satisfacción con la vida. Los valores en negrita indican significación en el nivel del 5%.

6.5 Artículo 5

6.5.1 Características basales de los pacientes

Para este estudio se reclutaron 660 pacientes. Veintiún pacientes fueron excluidos por no cumplir los criterios de inclusión. Esto resultó en una muestra final de 639 participantes, de los cuales 283 tenían cáncer torácico y 356 cáncer colorrectal, todos ellos en estadio avanzado e irresecables.

Las características demográficas y clínicas se muestran en la **Tabla 5.1**. La cohorte de cáncer torácico avanzado incluyó cáncer de pulmón (82 %, n = 232), esófago (15 %, n = 42) y pleura (3 %, n = 9). El grupo de cáncer colorrectal avanzado incluyó cáncer de colon (80%, n = 284), recto (18%, n = 64) e intestinal (2%, n = 8). Los sujetos con cáncer torácico eran predominantemente hombres (62 %) con una edad media de 65,6 años (desviación estándar = 9,5) y dos tercios tenían un cáncer en estadio IV (78 %). Las personas con cáncer colorrectal también eran principalmente hombres (61 %) con una edad media de 66,0 años (SD = 10,6) y la mayoría tenía un cáncer en estadio IV (85 %). No se revelaron diferencias significativas en la angustia psicológica respecto a la edad, el sexo, el estado civil y la educación en personas con cáncer torácico o colorrectal. (**Tabla 5.1)**

Tabla 5.1 Características demográficas basales (n=639)

Características basales	Cáncer torácico avanzado irresecable (*n*= 283)	Cáncer colorrectal avanzado irresecable (*n*= 356)
Edad (Media ± Desviación estándar)	65.6±9.5	66.0±10.6
Sexo (n, %)		
Hombre	176 (62)	218 (61)
Mujer	107 (38)	154 (39)
Estadio Civil		
Casado o con pareja	219 (85)	281 (86)
Soltero/viudo/divorciado	64 (15)	75 (14)
Educación		
≤ Primaria	112 (39)	185 (52)
> Secundaria	171 (61)	171 (48)
Empleado		
Si	147 (52)	199 (56%)
No (Jubilado o desempleado)	136 (48)	157 (44%)
Características clínicas		
Estadio (n, %)		
Localmente avanzado	63 (22)	54 (15)
IV	220 (78)	302 (85)
Histología		
Adenocarcinoma	146 (52)	300 (84)
Otras	137 (48)	56 (16)
Supervivencia estimada		
Más de 12 meses	70 (25)	101 (28)

Menos de 12 meses	213 (745)	255 (78)
Primer diagnóstico de cáncer		
No (recurrencia)	37 (13)	59 (16)
Si	246 (87)	297 (84)
Tratamiento sistémico (n, %)		
Quimioterapia	197 (70)	337 (95)
Otros sin quimioterapia	86 (30)	19 (5)

6.5.2 Detección de trastornos psicológicos

En total, 210 pacientes (74%) con cáncer torácico avanzado y 236 (66%) con cáncer colorrectal mostraron malestar psicológico según la escala BSI-18 que se consideró el estándar. La puntuación media del BSI-18 fue de 67,1 (DE = 7,5) en pacientes con cáncer torácico y 66,1 (DE = 7,1) entre los participantes con cáncer colorrectal avanzado. La precisión del EF-EORTC-QLQ-C30 para detectar malestar psicológico fue del 79 % en el grupo de cáncer torácico y del 76% en el grupo de cáncer colorrectal utilizando un punto de corte < 75. Se detectaron FP en 15 sujetos con cáncer torácico y 27 con cáncer colorrectal. Considerando estos FP, la especificidad fue del 79% en cáncer torácico y del 77% en cáncer colorrectal. Se detectaron FN en 44 sujetos con cáncer torácico y en 58 con cáncer colorrectal (**Figura 5.1**). Como resultado de estos FN, la sensibilidad fue del 79% en el cáncer torácico y del 75 % en el cáncer colorrectal.

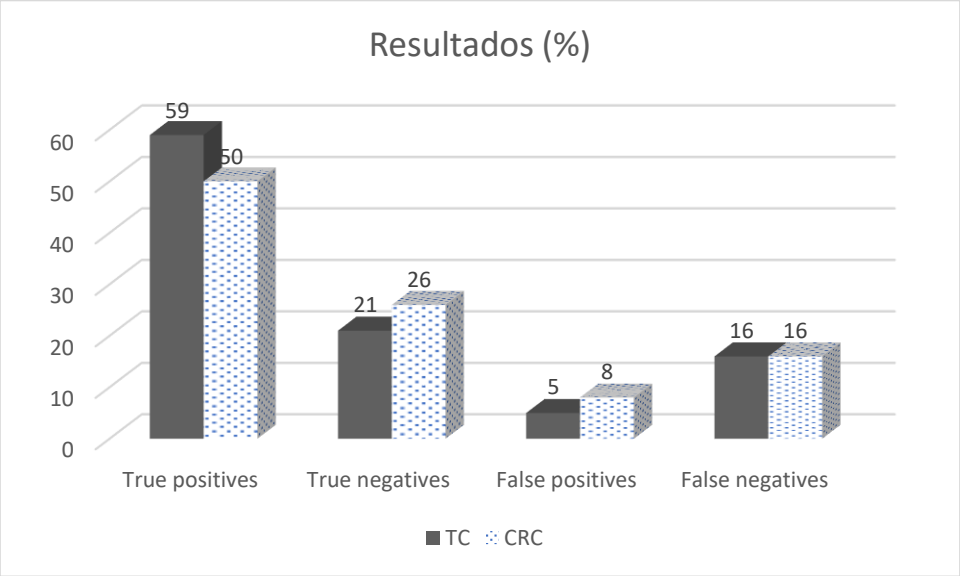

Figura 5.1 Resultados: verdadero positivo (TP), verdadero negativo (TN), falso positivo (PF) y falso negativo (FN) para el cáncer torácico avanzado (CT) irresecable y el cáncer colorrectal (CCR).

Además, el valor predictivo positivo fue del 92% para el cáncer torácico y del 87% para el cáncer colorrectal, mientras que el valor predictivo negativo fue del 56% para el cáncer torácico y del 61% para el cáncer colorrectal. El AUC para el cáncer torácico fue de 0,84 (IC 95%, 0,78–0,89) y de 0,85 (IC 95%, 0,80–0,89) para el cáncer colorrectal (**Tabla 5.2**).

Tabla 5.2 Detección de malestar emocional con la escala EF-EORTC-QLQ-C30

	Cáncer torácico avanzado irresecable (n=283)	**Cáncer colorectal Avanzado irresecable (n=356)**
Propiedades psicométricas		
Precisión	0.791	0.761
Sensibilidad	0.790	0.754
Especificidad	0.794	0.775
Valor predictivo positivo	0.917	0.868
Valor predictivo negativo	0.568	0.619
Área bajo la curva (AUC)*	0.73-0.86	0.71-0.82
(*) Relación entre EF-EORTC-QLQ-C30 y Brief Symptom Inventory 18 (BSI-18)		

Usando un punto de corte < 90 para el EF-EORTC-QLQ-C30, el valor predictivo positivo disminuyó tanto en el grupo de cáncer torácico como en el de cáncer colorrectal (89% y 83%, respectivamente), mientras que el valor predictivo negativo aumento en ambos (67% y 71%, respectivamente). Por lo tanto, el uso de un punto de corte < 75 parece funcionar mejor que < 90.

7. DISCUSION

7.1 Deterioro de la calidad de vida en pacientes oncológicos con cáncer avanzado

Uno de los principales objetivos de esta tesis fue analizar la calidad de vida de los pacientes con cáncer avanzado e identificar los factores que promueven su deterioro. A este respecto, en el **primer artículo** confirmamos una alta prevalencia de fatiga (55,7%) y de malestar emocional (47,7%) previo al inicio de terapia antineoplásica. Ambos factores, junto con la incertidumbre en torno a la enfermedad se asociaron con un empeoramiento de la calidad de vida de los pacientes. La variable clínica, estado general ECOG, y las variables demográficas, edad, sexo y comorbilidades, también afectaron negativamente la calidad de vida.

La fatiga es un síntoma habitualmente presente en los pacientes oncológicos y los estudios señalan una amplia variación en su prevalencia (rango 30-99%) [106–108]. En un estudio realizado en Italia, con una muestra de 1394 pacientes con cáncer, un 62% reportó fatiga, lo que impactó severamente en la calidad de vida en un tercio de los pacientes, dificultándoles su actividad diaria [109]. Nuestro estudio ha recogido un total de 508 pacientes de diferentes centros de España constatándose una prevalencia de fatiga del 55,7%.

En esta serie no se detectaron diferencias significativas entre pacientes con fatiga y mismo estado general ECOG en función de las comorbilidades ni entre la enfermedad localmente avanzada y metastásica. Dado que el estudio se realizó previo al inicio del tratamiento antineoplásico, es probable que dicha fatiga sea fruto de biomarcadores inmunes/inflamatorios, metabólicos, neuroendocrinos y genéticos relacionados con el cáncer [107]; que afectan por igual a los pacientes independientemente de su estado general.

La alta prevalencia de síntomas somáticos en estos pacientes provoca un deterioro de su estado funcional y aumenta la posibilidad de muerte en un corto período de tiempo [110–112]. En el **segundo artículo**, identificamos una

correlación negativa entre los síntomas físicos y el estado funcional, un hallazgo que concuerda con los estudios anteriores [113] y que perjudica a la salud psicológica y la calidad de vida de los pacientes.

El 41% de los participantes reportaron dificultades para realizar actividades cotidianas. De acuerdo con una revisión sistemática (n=43 estudios), entre el 36,7% y el 54,6% de los pacientes con cáncer refieren dificultades para realizar tareas básicas y esenciales del día a día [114], las cuales tienden a empeorar con el tiempo [115]. La identificación temprana de grupos de pacientes con alto riesgo de deterioro funcional podría ayudar a plantear intervenciones como la atención médica domiciliaria, programas de ejercicio para pacientes hospitalizados, rehabilitación y programas de promoción de la salud. Estas intervenciones podrían ayudar a los pacientes a manejar sus síntomas y mejorar su estado funcional [116–118].

Asimismo, en la muestra analizada en el **primer artículo** la prevalencia de malestar psicológico fue del 48%. Al igual que sucede con la fatiga, estos datos no se ven influenciados por el número y tipo de comorbilidades. Analizando en detalle los síntomas psicológicos más relevantes (depresión y ansiedad) se ha visto en diversos estudios que el sexo femenino y la enfermedad avanzada son dos de los factores de riesgo más prominentes para desarrollar malestar psicológico, ya sea en forma de depresión o ansiedad [119–121]. En este sentido, en el **segundo artículo** observamos que la prevalencia de síntomas de depresión en nuestra muestra fue del 44,3%, superior a la de sujetos españoles con cáncer resecado (36,6%) [28], y muy superior a la de la población general española (4,7%) [122]. Esto sugiere que la presencia de síntomas depresivos es alta entre las personas con cáncer, particularmente en aquellas con metástasis.

Los factores sociales también pueden desempeñar un papel importante en el estado emocional de los pacientes [110,123]. En nuestra serie, las mujeres, los

individuos más jóvenes, las personas solteras o sin pareja y las personas con cáncer recurrente presentaron más síntomas de depresión en comparación con los hombres, los pacientes mayores, las personas casadas y las que se enfrentaban al cáncer por primera vez. Este hallazgo concuerda con publicaciones previas [124–126]. Las altas tasas de depresión, especialmente en ciertos grupos, resaltan la necesidad de que los profesionales sanitarios diseñemos e implementemos estrategias efectivas para evaluar y mitigar los síntomas depresivos en casos de cáncer avanzado, mejorando así su salud mental.

En resumen, tanto el **primer como el segundo artículo** reflejan una alta prevalencia de síntomas somáticos y psicológicos en pacientes con cáncer avanzado, los cuales se asocian con una disminución en la calidad de vida.

7.2 Estrategias de afrontamiento y toma de decisiones

Los pacientes oncológicos tienden a presentar una mayor prevalencia de síntomas psicológicos, los cuales se pueden intensificar debido al deterioro físico y funcional que experimentan. En el **segundo artículo** hemos examinado la relación entre este estado funcional y los síntomas depresivos y como estos se modulan por las estrategias de afrontamiento que los pacientes adoptan.

Las estrategias que los pacientes emplean para lidiar con su enfermedad pueden aliviar el estrés o malestar psicológico causado por su declive funcional durante esta etapa de la vida [127,128]. Hemos observado que las estrategias de afrontamiento positivas les ayudan a mantener la confianza en adaptarse a esta nueva situación, lo que se refleja en un mejor estado de ánimo. Por otro lado, las estrategias de afrontamiento negativas, como la preocupación ansiosa o la desesperanza, tienden a exacerbar los síntomas depresivos.

En otras palabras, el ajuste mental, principalmente la presencia de estrategias de afrontamiento negativas actúa como un filtro que modula cómo los pacientes perciben los cambios en su estado funcional, especialmente si estos son adversos, generando angustia y señal de declive de su situación, lo que a su vez puede aumentar síntomas como la depresión. Esta relación entre la actitud negativa y la depresión ha sido documentada en otros estudios [129,130] así como su conexión con una mayor sensibilidad al dolor [131] y una menor supervivencia [132].

Es importante destacar que las estrategias de afrontamiento de los pacientes son dinámicas y pueden variar según el momento de la enfermedad. La cantidad de información que el paciente recibe puede influir en estas estrategias; por ejemplo, los pacientes con menor conocimiento sobre el pronóstico de su enfermedad tenderán a adoptar estrategias de evitación cognitiva y los más informados tenderán a adoptar estrategias negativas.

A este respecto, en el **tercer artículo** hemos visto como los pacientes con un mayor conocimiento sobre el pronóstico de su enfermedad tendían a mostrar un aumento de síntomas psicológicos, con el consecuente deterioro de calidad de vida que ello conlleva. Estos hallazgos son congruentes con los obtenidos en otros estudios [75,76].

Históricamente se ha descrito que los sujetos bien informados, suelen aceptar la irreversibilidad del proceso y optar por no recibir tratamiento o, por el contrario, incrementar su interés por la terapia en lugar de rechazarla. Nuestros datos apuntan a que una alta precisión en el pronóstico de la enfermedad tuvo un efecto pequeño pero favorable en nuestros pacientes hacía terapias de bajo beneficio. Este interés por terapias de baja eficacia aumentó consistentemente en pacientes que mantenían una creencia en la curabilidad, miedo a la muerte y mayor apoyo social. Resultó especialmente sorprendente el gran interés manifestado por los pacientes de edades extremas. En ancianos el interés puede deberse al impacto

del factor sociofamiliar con mayor colusión y generación de falsas esperanza, o bien reflejar un cambio de tendencia en una sociedad envejecida, con mayores de 70 años físicamente activos, con expectativa de gozar de buena salud durante años.

Nuestro análisis sugirió que, por cada 10 pacientes con consciencia pronóstica correcta, solo uno rechazaría recibir terapias de baja eficacia, a costa de que al menos dos sufrieran depresión, o uno tuviera un deterioro significativo de calidad de vida significativo.

Este hallazgo nos plantea un dilema ético. Aunque debemos respetar el derecho a la información que presentan los pacientes, no podemos pasar por alto el impacto negativo que dicha información puede desencadenar en ellos, ya que podría provocar un aumento de los síntomas depresivos y un deterioro de calidad de vida, sin disminuir de manera significativa el interés por terapias de bajo beneficio.

Esta cuestión es aún más debatible teniendo en cuenta el bajo impacto que tuvo la información pronóstica en nuestros pacientes. En este estudio encontramos que, tras la primera visita con un oncólogo, el 74% de los pacientes con cáncer avanzado incurable mantienen la creencia en la posibilidad de curación. Dos tercios de los pacientes recibieron información cualitativa sin alusión a la muerte, y el tercio restante cualitativa con alusión a la muerte, presentando estos últimos una creencia en la curabilidad del 45%. La interpretación de esta dinámica conlleva una mezcla de optimismo de los oncólogos y pacientes que, de alguna manera, desean y no desean escuchar su sentencia de muerte y mitigan su angustia a través de rutinas centradas en el calendario de la quimioterapia, sin llegar a asimilar completamente la información pronóstica antes de la progresión. Es posible también que el miedo focalice la atención en el corto plazo o haga olvidar los detalles de las entrevistas.

Este miedo a dañar contribuye a la falta de consenso sobre las técnicas más adecuadas para comunicar el pronóstico de la enfermedad, y apoya la actitud prudente de los oncólogos. Sin embargo, es evidente que la transmisión de esta información es un proceso largo que no puede intentar resolverse en la primera visita.

7.3 Influencia del tratamiento en la calidad de vida

Teniendo en cuenta el deterioro en calidad de vida que presentan los pacientes oncológicos y como se modula en función de diversos factores inherentes al paciente y al oncólogo, en el **cuarto artículo** optamos por examinar cómo influye el tratamiento oncológico en esta calidad de vida. Para ello, estudiamos dos poblaciones: los pacientes con un cáncer avanzado irresecable y los pacientes con un cáncer localizado resecado.

En este estudio notamos que los pacientes con cáncer avanzado presentan una peor calidad de vida y una menor satisfacción con la vida tras el diagnóstico del cáncer, y previamente al inicio del tratamiento antineoplásico, que los pacientes con un cáncer localizado y resecado (curado). En la segunda evaluación, tras recibir tratamiento antineoplásico sistémico, ambas poblaciones experimentan un empeoramiento de la calidad de vida siendo este significativamente mayor en la población con cáncer localizado frente a la de cáncer avanzado.

La peor calidad de vida en los pacientes de nuestra serie con un cáncer avanzado previo al inicio del tratamiento antineoplásico, en comparación con los pacientes con un cáncer localizado, se debe a la presencia de más síntomas físicos, encontrándose una alta prevalencia de fatiga y dolor, de forma similar a las referidas en otros estudios [10,133]. Asimismo, se observa una mayor prevalencia de disnea, insomnio, pérdida de peso, estreñimiento y diarrea. Esto es esperable, dado que los pacientes con cánceres avanzados presentan el cáncer primario y

metástasis, que afectan a múltiples órganos y funciones orgánicas, llevando a la aparición de dichos síntomas. Por otro lado, la otra cohorte no presenta enfermedad neoplásica ya que se ha resecado. En este grupo, los síntomas más exacerbados son el insomnio, la fatiga y la pérdida de apetito que podrían explicarse por secuelas tempranas de la cirugía [134].

Por otra parte, también hemos observado que previo al inicio del tratamiento, los pacientes con enfermedad avanzada presentan mayor limitación funcional a nivel emocional, cognitivo y social. Esto se explica por un peor afrontamiento de la enfermedad, la mayor parte de las veces incurable, enfrentándose a un proceso psicológico más complejo [27], así como al deterioro de la calidad de vida debido a una mayor presencia de síntomas somáticos, que en conjunto les limita a la hora de desarrollar su vida social habitual [10]. Secundario a todo esto hemos encontrado una mayor satisfacción vital, previo al inicio del tratamiento, en los pacientes con enfermedad localizada.

Tras el primer estudio de imagen de evaluación de respuesta (cohorte con cáncer avanzado) y tras finalizar el tratamiento adyuvante (cohorte con cáncer localizado), se produce un empeoramiento importante en todas las escalas analizadas, así como un aumento de todos los síntomas en los pacientes con enfermedad localizada. Hay que considerar que el objetivo del tratamiento en estos pacientes es la curación y la disminución del riesgo de recurrencia y, puesto que el logro es mayor que en la cohorte de enfermedad avanzada, se acepta administrar tratamientos efectivos con elevada toxicidad asumiendo un detrimento temporal en la calidad de vida [135]. Sin embargo, es importante tener en cuenta que, en varios estudios, se ha constatado que algunos efectos adversos del tratamiento tienen repercusiones a largo plazo en estos pacientes [136,137].

En los pacientes con una enfermedad avanzada se ve un deterioro de una magnitud mucho menor, con cambios mínimos en las diferentes escalas. Se ha estudiado el punto de corte (cut-off) que determina la relevancia clínica de los

cambios que sufren los pacientes oncológicos, arrojando diferentes valores según el autor, todos ellos mayor a los presentados por la población con enfermedad avanzada de este estudio, concluyendo que no presentan cambios clínicos relevantes [138–141]. Esta ausencia de cambios clínicos relevante se explica dado que se les administra un tratamiento antineoplásico con el fin de aumentar la supervivencia haciendo énfasis en preservar la calidad de vida en esta población, disminuyendo la carga tumoral y los síntomas relacionados con esta mediante los tratamientos. La mejora de la calidad de vida tras la quimioterapia ya se ha observado en otros estudios [142]. Si bien el tratamiento antineoplásico puede producir toxicidad, la reducción de la carga tumoral, así como un mayor cuidado en la evaluación del balance riesgo-beneficio de los tratamientos para evitar toxicidades graves, explican esta ausencia de cambio en este grupo.

Todo esto redunda en un empeoramiento del estado de salud en los pacientes con cáncer localizado al finalizar el tratamiento adyuvante, lo cual debe tenerse en cuenta en el seguimiento posterior a estos pacientes curados, pero con secuelas que podrían dificultar su inserción social y laboral. Por su parte, en pacientes con cáncer avanzado presentan una calidad de vida preservada tras iniciar el tratamiento antineoplásico probablemente en relación con un control de su enfermedad tumoral y un mejor balance beneficio-toxicidad por parte del oncólogo en esta población.

Queda reflejada la necesidad de ampliar estudios a este respecto, identificando los subgrupos con mayor riesgo de deterioro de la calidad de vida y aumento de los síntomas psicológicos. Esta selección podría ayudar a la implementación de estrategias tempranas de promoción de la salud con el fin de disminuir las repercusiones y mejorar la calidad de vida de los pacientes durante todo el proceso.

Esto último resulta extremadamente difícil debido a la falta de tiempo y medios que presentan la mayoría de los profesionales en su trabajo diario. En aras de

buscar una solución, en el **quinto artículo** hemo validado una herramienta simple y efectiva para detectar el malestar psicológico en pacientes con cáncer avanzado que muestra una precisión del 71% y 75% para pacientes con cáncer torácico y colorrectal, respectivamente.

Aunque existen escalas validadas para medir este parámetro, la mayoría de ellas son complejas y de difícil aplicación, siendo necesaria una escala rápida y simple como la EF-EORTC-QLQ-C30 para su aplicación de forma más rutinaria.

En nuestra muestra, esta escala tiene una sensibilidad del 66% y 68% y una especificidad del 86% y 88% para cáncer torácico y colorrectal, respectivamente, considerando el BSI-18 como estándar de medición.

7.4 Limitaciones del estudio

Los estudios realizados dentro de esta tesis doctoral cuentan con varias limitaciones. En primer lugar, se han analizado pacientes con diferentes características, y aunque hemos considerado múltiples variables basales y ajustado los análisis por estado general, edad y tipo de tumor, no podemos descartar que alguna variable no que no haya sido considerada haya podido influir en los resultados. En segundo lugar, el estudio se realizó en población oncológica española y se requiere de precaución a la hora de trasladar nuestros resultados a otros países, especialmente no occidentales, ya que la atención al cáncer depende de la organización del sistema sanitario y de la economía del país, existiendo en España una sanidad pública de acceso universal. En tercer lugar, durante el transcurso del estudio se ha perdido el seguimiento de numerosos pacientes, fundamentalmente debido al deterioro clínico o fallecimiento de los pacientes, lo que representa una pérdida de información en

el subgrupo de pacientes más deteriorados. Por último, los cuestionarios fueron rellenados por el paciente sin supervisión directa del investigador.

7.5 Implicaciones clínicas y perspectivas de investigación futura

Las conclusiones obtenidas en la presente tesis doctoral, aun con las limitaciones antes mencionadas, plantean implicaciones clínicas relevantes y apuntan hacia nuevas direcciones para la investigación futura en el área del cáncer.

Primordialmente, se resalta la necesidad de implementar un enfoque más integral y personalizado en la atención de pacientes oncológicos. Esto incluye no solo atender los aspectos moleculares, clínicos y físicos de la enfermedad, sino también reconocer y abordar los factores psicológicos y emocionales que pueden afectar la calidad de vida del paciente.

En este sentido, se subraya la importancia de la comunicación paciente-oncólogo y del manejo apropiado de la información pronóstica. Es crucial que los oncólogos estén conscientes de que, aunque el conocimiento de la verdad puede ofrecer a los pacientes una sensación de control y de capacidad de decidir mejor sobre el interés de recibir tratamiento antineoplásico, también puede tener el potencial de empeorar su bienestar psicológico y su capacidad de afrontamiento.

Este delicado balance entre honestidad y consideración es crucial para orientar a los pacientes en su travesía con el cáncer, considerando cuándo es el momento óptimo para compartir información específica acerca de su enfermedad.

A su vez, los resultados ponen de relieve la importancia de una detección temprana y eficaz del malestar psicológico en pacientes con cáncer avanzado. La validación de una herramienta simple y eficaz, tal como la EF-EORTC-QLQ-

C30, puede facilitar este proceso y se podría proponer su incorporación en la práctica clínica habitual.

En términos de investigación futura, se hace necesario expandir y profundizar en los estudios sobre el impacto del tratamiento oncológico en la calidad de vida del paciente, identificando aquellos subgrupos con mayor riesgo de deterioro y síntomas psicológicos. Esto podría orientar el desarrollo de estrategias tempranas y personalizadas de promoción de salud, con el fin de minimizar las repercusiones y mejorar la calidad de vida de los pacientes durante todo el proceso.

Por último, es indispensable que se realicen investigaciones en diversas poblaciones y contextos, para garantizar la generalización y aplicabilidad de los resultados obtenidos. Se debe considerar la diversidad cultural y geográfica, así como las variaciones en los sistemas de atención de la salud a la hora de adaptar y aplicar las estrategias de atención y las herramientas de evaluación.

Estos hallazgos deben orientarnos hacia la mejora constante del cuidado oncológico para maximizar la calidad de vida del paciente durante toda la evolución de su enfermedad.

8. CONCLUSIONES

Teniendo en cuenta estos resultados dividimos las conclusiones de esta tesis de acuerdo con los cinco artículos que la componen:

1) Los pacientes con cáncer avanzado presentan niveles significativos de fatiga y angustia psicológica después del diagnóstico, los cuales afectan negativamente a su calidad de vida. Asimismo, se encontró una alta prevalencia de incertidumbre en torno a la enfermedad. Sin embargo, no pudimos establecer una relación independiente entre esta incertidumbre y la disminución de la calidad de vida.

2) Los resultados de nuestro estudio confirman la correlación entre el estado físico y la depresión; evidenciando que un buen estado funcional puede repercutir favorablemente en el estado mental del paciente. Adicionalmente, se identificó que los estilos de afrontamiento caracterizados por desesperanza, preocupación ansiosa y angustia pueden potenciar el impacto negativo del estado funcional en la depresión.

3) Nuestra investigación indica que los malentendidos sobre el pronóstico de la enfermedad neoplásica son frecuentes en la era de la inmunoterapia y terapias dirigidas. Estos malentendidos repercuten en el estado de ánimo y condicionan la toma de decisiones informadas.

4) El tratamiento antineoplásico sistémico puede ser útil no solo para prolongar la supervivencia de los pacientes con un cáncer avanzado irresecable, sino también para preservar su calidad de vida. Por otro lado, observamos como los pacientes con enfermedad localizada son sometidos a tratamientos complementarios con intención curativa que pueden tener un impacto negativo en su calidad de vida.

5) La subescala EF-EORTC-QLQ-C30 es una herramienta breve y útil, con un punto de corte definido, para identificar pacientes con cáncer torácico y colorrectal avanzado con problemas emocionales que podrían beneficiarse de atención especializada.

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10. ARTICULOS

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Fatigue, Emotional Distress, and Illness Uncertainty in Patients with Metastatic Cancer: Results from the Prospective NEOETIC_SEOM Study

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Abstract: A cancer diagnosis can have a substantial impact on a patient's mental health and quality of life. The aim of this study was to investigate the prevalence of fatigue, emotional distress, and uncertainty and examine the predictive value they have on the quality of life of advanced cancer patients. A prospective, multicenter study was conducted between February 2020 and May 2021 of individuals diagnosed with an advanced, unresectable neoplasm prior to initiating systemic antineoplastic treatment. Participants completed questionnaires to quantify fatigue, emotional distress, disease uncertainty, and quality of life. A linear regression analysis was performed to study the predictive QoL variables. The study population comprised 508 patients, 53.7% of whom were male and had a mean age of 54.9 years. The most common cancers were digestive (40.6%), bronchopulmonary (29.1%), and breast (8.5%); the most frequent histology was adenocarcinoma (63%); and most were stage IV (79.7%). More than half (55.7%) suffered fatigue, and 47.7% exhibited emotional distress; both were more prevalent among women. Fatigue, emotional distress, and disease uncertainty all correlate with diminished quality of life. Similarly, ECOG performance status and the demographic variables of age, sex, and comorbidities impacted quality of life. This patient sample displayed a high prevalence of fatigue and emotional distress, together with illness uncertainty, which are clearly linked to waning quality of life. To decrease the experience of fatigue and improve mental health treatment in cancer patients, interventions based on a biopsychosocial model must be intensified.

Keywords: quality of life; fatigue; emotional distress; uncertainty; cancer; antineoplastic treatment

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1. Introduction

Cancer is a public health problem in our society with an ever-growing incidence, with estimates of some 21.6 million new cases by 2030 [1]. A major consideration when addressing this disease is the considerable negative repercussions for patients' quality of life (QoL), due to the disease process itself, its treatment, and its duration [2]. Though not generally quantified, economic, social, and family aspects also affect their QoL but are not generally measured Such is the case from the very onset of disease, lasting throughout treatment and the final stage of illness [3].

WHO defined quality of life as the individual's perception of the place they occupy in the cultural setting and in the system of values where they live, as well as with respect to their goals, expectations, criteria, and concerns; all tempered by their physical health, psychological state, degree of independence, social relations, environmental factors, and their personal beliefs [4]. Similarly, QoL can be conceptualized as a subjective perception that encompasses all the patient's facets and needs, constantly evaluating the differences between the individual's actual situation and their ideal situation at any given time. Thus, it is a dynamic path that changes over time [5,6].

Specifically, individuals with advanced cancer experience a variety of persistent, unpleasant, and highly limiting physical and psychological symptoms that negatively impact their QoL. These patients commonly exhibit weight loss, fatigue, and pain [7,8]. Depending on the type of tumor, certain symptoms prevail over others; thus, in people with lung cancer, dyspnea, fatigue, and cough are the most frequent [9], whereas in gastrointestinal neoplastic disease, fatigue, pain, and weight loss are the most prevalent [10]. Likewise, breast or gynecological cancers are accompanied most often by psychological symptoms, such as stress, depression, and sexual alterations, in addition to a high prevalence of fatigue [11,12].

Cancer-related fatigue is one of the most prevalent symptoms patients suffer both during and after treatment [13,14], affecting 50–90% of all cases [14–16]. Fatigue appears regardless of age, sex, type of cancer, stage of disease, and treatment modality [15,17,18] and can become persistent, thereby limiting QoL and the activities of daily life for years [13,14,16]. Moreover, cancer-associated fatigue is unlike the exhaustion that most people experience as a result of their daily activities, inasmuch as it is not proportional to the level of effort and rest or sleep fail to remedy it [14,18]. Not only does it impair QoL, but it also restricts the person's physical and social activities and their ability to return to work [14,16].

Until recently, fatigue in patients with cancer was neglected, and more attention was given to symptoms such as nausea and pain [19,20]. One of the reasons why fatigue has gone unnoticed is the variety of factors that can contribute to its development and conceal it, such as what is known as the general cancer syndrome, the direct consequence of the neoplasm or its treatment on the central nervous system or muscle energy metabolism, sleep or circadian rhythms, stress, despondency or depression, immune activation, anemia, cachexia, or malnutrition, etc. [21–23]. Likewise, despite its high prevalence and possible interference with activities and patients' wellbeing, research into the etiopathogenesis of and approaches to fatigue in patients with metastatic cancer is meager.

Furthermore, individuals with advanced cancer display a high prevalence of emotional distress that varies depending on age and type of cancer; nonetheless, overall, emotional problems are found in more than 30% of all oncological patients [24]. Depression and anxiety are common symptoms among patients with cancer, with rates ranging between 11% and 57% for depression and between 6.5% and 23% for anxiety [14,25,26]. These psychological issues have been found to be affected by 5 main symptoms: anxiety, depression, fear of dying, demoralization, and the inability to cope with the disease. All appear in relation to the strain of the treatment they must deal with and translate into worse QoL, worse functional status, increased suicide rates, and early death [27].

Uncertainty is another pressing aspect of cancer patients' journeys and can cause them to experience a prolonged feeling of loss of control, having a direct, negative impact on how they cope with cancer, their psychological wellbeing, and QoL. In fact, cancer and the uncertainty surrounding its evolution are associated with psychological distress in up to 30–50% of the cases [15,25,28–31]. Some studies have revealed a prevalence of uncertainty surrounding the disease in up to 60% of the oncological population [32]. In patients with an advanced, unresectable cancer, uncertainty is the wellspring of the inability to predict the course of the neoplasm with any certainty, of the perception of the future as threatening, of the advanced status of the process, and/or of communication barriers (conspiracy of silence, emotional blockage, cultural level, the healthcare professional's

ability, etc.). Numerous studies have linked clinical uncertainty with diminished QoL and resilience, anxiety, depression, and other negative effects.

Given the widespread presence of cancer, those factors that, from the very beginning of the disease, might be associated with impaired QoL must be identified. This will make it possible to plan actions that maximize the factors that can positively affect patients' QoL so as to prevent, eliminate, or minimize those that contribute to its worsening.

In this context, the objective of this study is to analyze the prevalence of fatigue, emotional distress, and uncertainty in patients with metastatic cancer and to examine the predictive value of fatigue, emotional distress, and uncertainty in these patients' QoL. This analysis has been conducted in a sample of individuals with recently diagnosed, advanced cancer prior to initiating antineoplastic treatment to determine the prevalence of these symptoms at the beginning of the disease, as well as how they relate to the decline in QoL these individuals display at the beginning of their cancer journey. We expect to find high levels of fatigue, emotional distress, and uncertainty among the participants, and that the factors explored in this study account for a portion of the variance in QoL.

2. Materials and Methods

2.1. Study Design and Population

This study is part of the prospective, consecutive NEOetic registry executed in 15 hospitals in Spain between February 2020 and May 2021. After attaining informed consent in writing, all the participants that were treated at the medical oncology departments at these centers and had a confirmed diagnosis of an advanced neoplasm were invited to participate at their first appointment with the oncologist, during which they were informed of their diagnosis and the antineoplastic treatment to be administered.

Patients eligible for surgery or other therapies with curative intent, those whose physical condition, comorbidities, and/or age comprised a contraindication for antineoplastic treatment in the opinion of the treating oncologist, anyone who had been treated for another advanced cancer in the previous two years, or whose underlying personal, family, sociological, and/or medical condition might hinder their ability to participate in the study, were excluded. This investigation was conducted in accordance with the standing ethical principles and received prior approval by the ethical review boards of each institution and by the Spanish Agency for Medicines and Medical Devices (AEMPS; ID Code: ES14042015). The study involved filling out several questionnaires and gathering clinical data from the individual's interview and their medical record. The procedures for collecting data were similar at all the hospitals, and the data regarding the participants were obtained from the centers where they received treatment. Participation was voluntary, anonymous, and in no way affected patient care. Data were collected and updated by the medical oncologist by means of a web platform (www.neoetic.es, accessed on 12 June 2021).

2.2. Description of Variables

Sociodemographic characteristics were collected using a standardized self-report form. Information concerning the subjects' disease was obtained by the attending oncologist by reviewing their medical record. The person's general status was assessed as per the Eastern Cooperative Oncology Group (ECOG) performance scale, with values ranging from zero (asymptomatic) to five (deceased). Any value was admitted as long as the oncologist deemed the patient eligible to receive systemic treatment. The oncologist gave the participants the questionnaire during the course of the appointment, and the patient filled it out at home prior to beginning systemic cancer treatment.

Quality of life was measured with the QLQ-C15 PAL questionnaire [33], which comprises 15 items for the assessment of two multi-item functional scales, two symptom scales with multiple items each, five single-item symptom scales, and a question on global health status. For the purposes of this study, items 7 and 11 were eliminated, as they are similar to the one that refers to fatigue. This scale has been validated in multiple languages, including

Spanish [34]. The total scale score ranges from 0 to 100; the higher the score, the better their QoL. In this sample, Cronbach's alpha for the scale was 0.87.

Fatigue was gauged using the three-item Health-related QoL (HRQoL) fatigue scale and the EORTC QoL QLQ-C30 questionnaire (version 3.0), which has been validated in Spanish [35,36]. The questionnaire consists of three simple questions: "Did you need rest?", "Have you felt weak?", and "Were you tired?". The items were converted to a rating scale from 0 to 100. According to the thresholds of clinical importance (TCIs), the values recommended by Giesinger et al. [37] for the fatigue scale were $\geq$39. In this study, Cronbach's alpha for the scale was 0.88.

Emotional distress over the past 7 days was determined by the 18 items of the Brief Symptom Inventory (BSI), one of the most commonly used instruments for this purpose [38]. Raw scores are converted to T-scores based on gender-specific, normative data. To identify individuals with significant levels of emotional distress, the BSI applies the clinical case rule [38], originally developed for SCL-90. Based on the cut-off values recommended by Derogatis [38], patients whose T score $\geq$67 were deemed to suffer "possible emotional distress". The Spanish version of the BSI has demonstrated good reliability and validity among Spanish cancer patients [39]. Cronbach's alpha varied from 0.81 to 0.90 [38].

Uncertainty of Illness was computed by means of the 5-item Mishel Uncertainty of Illness Scale (MUIS) validated for the Spanish population [40–42]. This questionnaire appraises reactions to uncertainty, ambiguity, and the future. Items are scored on a Likert scale ranging from 1 (the patient does not exhibit any of the characteristics described in the item at all) to 5 (the patient displays the highest degree of the described characteristic), yielding possible scores of 5 to 25, with higher scores corresponding to greater uncertainty. Patients whose T score $\geq$16 were deemed to suffer "uncertainty". Cronbach's alpha was 0.83 [40].

The questionnaires were given to the participants after the study was explained to them and they agreed to participate and signed the informed consent form, and after shared oncologist-patient decision making regarding systemic oncological treatment for incurable, advanced cancer. Patients completed the questionnaires at home and gave them to their oncologist at their following appointment, coinciding with the start of antineoplastic treatment.

2.3. Statistical Methods

Descriptive statistics, means, and standard deviations (SD) were calculated for the sample's demographic and clinical characteristics. A bivariate chi-square was used to examine differences between fatigue and emotional distress according to sex and disease stage. Pearson's correlation coefficient was calculated to gauge the association of QoL with fatigue, emotional distress, and disease uncertainty. Multicollinearity across variables was rejected by the variance inflation factor being <5 for all and the tolerance >0.2 [43]. To ascertain the predictive variable of QoL, a two-block linear regression model was carried out. In the first block, fatigue, emotional distress, and disease uncertainty were recorded as criterion variables. In the second block, sex and age were entered as independent variables. We applied R-squared and Cohen's standardized f2 measure of effect size to interpret the data [44]. For all analyses, significance was set at $\alpha < 0.05$. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software, version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA: IBM Corp.).

3. Results

3.1. Population Description

This study population consisted of 508 patients, of whom 273 (53.7%) were male, the mean age was 54.9 years (SD = 10.1), and 49.6% were elderly (>70 years). Most were married or had a partner (83.1%) and/or children (83.7%). Less than half (47.8%) had a primary education level. As for employment status, all were retired or unemployed. The most common cancers were digestive (40.6%), bronchopulmonary (29.1%), and breast

(8.5%). The most common histology was adenocarcinoma (63%) and most neoplasms were stage IV (79.7%); the remaining were unresectable stage III. The most frequently administered treatments were chemotherapy (55.7%), chemotherapy with targeted therapy (10.6%), and chemotherapy with immunotherapy (9.6%). In 26.2% of participants, the treatment decision was informed by the presence of a molecular biomarker. Estimated survival was <18 months in 48.8% of the sample (see Table 1).

Table 1. Cancer types, stages, and medical comorbidities of patients (n = 508).

Variables	N	%
Sex		
Female	235	46.3
Male	273	53.7
Age (years)		
<45	17	3.4
45–70	239	47.0
>70	252	49.6
ECOG		
0	174	34.3
1	300	59.1
2	31	6.1
3	3	0.6
Comorbidities		
Cardiovascular disease	206	40.6
Chronic illness	11	2.2
Psychiatric disorder	21	4.1
Cardiovascular + chronic disease	34	6.7
Cardiovascular + chronic disease + psychiatric disorder	17	3.3
Obesity (body mass index ≥30)	80	15.7
Weight loss	69	13.6
Other comorbidities	70	13.8
Marital status		
Married or partnered	335	83.1
Single/divorced/widowed	68	16.9
Educational level		
Primary	243	47.8
High school or more	265	52.2
Children		
With children	425	83.7
Without children	83	16.3
Tumor site		
Broncho-pulmonary	148	29.1
Digestive	206	40.6
Gynecological and breast	43	8.5
Others	111	21.9
Histology		
Adenocarcinoma	320	63.0
Others	188	37.0
Stage		
Locally Advanced	103	20.3
Metastatic Disease (IV)	405	79.7
Biomarker for treatment decisions		
No	375	73.8
Yes	133	26.2
Survival		
<18 months	248	48.8
≥18 months	260	51.2

Table 1. *Cont.*

Variables	N	%
Type of treatment		
Chemotherapy	283	55.7
Chemotherapy and immunotherapy	49	9.6
Chemotherapy and targeted drug	54	10.6
Immunotherapy	35	6.9
Targeted drug	28	5.5
Others	58	11.4

3.2. Prevalence of Fatigue and Emotional Distress

All told, 283 (55.7%) subjects expressed experiencing fatigue (score $\geq$ 39), as per Giesinger et al. [37]. Females exhibited more fatigue than males (χ^2 = 11.689; p < 0.001). Emotional distress was present in 47.7% of the population (T score $\geq$ 67), according to the cut-off values recommended by Derogatis [38]. Women displayed greater emotional distress than men (χ^2 = 6.347; p = 0.012) (see Table 2). Uncertainty was present in 36.4% of the study population (PD $\geq$ 16). Patients with other comorbidities (such as chronic illness or psychiatric disorder) displayed greater uncertainty than those with comorbid cardiovascular disease (χ^2 = 7.150; p = 0.007); patients with a worse ECOG presented more uncertainty (χ^2 = 9.155; p = 0.027). No differences were detected with respect to the incidence of fatigue, emotional distress, or uncertainty across stages or comorbidities (see Table 2).

Table 2. Fatigue and emotional distress across sexes and stage types.

Variables	Fatigue		Emotional Distress		Uncertainty	
	None (FA < 38.9)	Fatigue (FA $\geq$ 39)	None (ED < 66.9)	Em. Distress (ED $\geq$ 67)	None (UN < 15.9)	Fatigue (UN $\geq$ 16)
Sex (*n*, %)						
Male	140 (62.2)	133 (47.0)	155 (58.7)	113 (47.5)	172 (53.3)	101 (37.0)
Female	85 (37.8)	150 (53.0)	109 (41.3)	125 (52.5)	151 (46.7)	84 (45.4)
p-value	<0.001 *		0.012 *		0.770	
Stage type (*n*, %)						
Locally advanced	40 (17.8)	63 (22.3)	57 (21.6)	45 (18.9)	61 (18.9)	42 (22.7)
Metastatic	185 (82.2)	220 (77.7)	207 (78.4)	193 (81.1)	262 (81.1)	143 (77.3)
p-value	0.212		0.577		0.303	
Comorbidities (*n*, %)						
Cardiovascular disease	112 (49.8)	142 (50.2)	131 (49.6)	119 (50.0)	176 (54.5)	78 (42.2)
Others	113 (50.2)	141 (49.8)	133 (50.4)	116 (50.0)	147 (45.5)	107 (57.8)
p-value	0.929		0.932		0.007 *	
ECOG (*n*, %)						
0	104 (46.2)	70 (24.7)	101 (38.3)	70 (29.4)	121 (37.5)	53 (28.6)
1	113 (50.2)	187 (66.1)	151 (57.2)	147 (61.8)	187 (57.9)	113 (61.1)
2	7 (3.1)	24 (8.5)	10 (3.8)	20 (8.4)	13 (4.0)	18 (9.7)
3	1 (0.4)	2 (0.7)	2 (0.8)	1 (0.4)	2 (0.6)	1 (0.5)
p-value	0.001 *		0.046 *		0.027 *	

FA = Fatigue; ED = Emotional Distress. * These values indicate significance at the 5% level.

3.3. Relationship of Fatigue, Emotional Distress, and Uncertainty of Illness with Quality of Life

In an initial analysis of bivariate correlations, fatigue, emotional distress, disease uncertainty, and ECOG performance status were seen to be significantly associated with QoL (correlations of −0.23 to −0.71, all p < 0.001; Table 3). A linear regression analysis contemplating fatigue, emotional distress, illness uncertainty, and ECOG status as predictors, together with the demographic variables of age, sex, and comorbidities, evinced a significant (statistical, non-causal) influence of fatigue, emotional distress, illness uncertainty, and ECOG status on QoL (F = 129.50, p <0.001). This model revealed high explanatory power

(adjusted R^2 = 0.61 for the model), in keeping with Cohen's guidelines [44] (f2 = 1.60). More symptoms on these scales were associated with worse QoL (see Table 4).

Table 3. Correlations of fatigue, emotional distress, and illness uncertainty with QoL.

Variables	Fatigue	Emotional Distress	Illness Uncertainty	ECOG	Quality of Life
Fatigue	1				
Emotional distress	0.559 **	1			
Illness uncertainty	0.177 **	0.264 **	1		
ECOG	0.237 **	0.129 **	0.105 *		
Quality of life	−0.705 **	−0.645 **	−0.298 **	−0.251 **	1

** $p < 0.001$; * $p < 0.005$.

Table 4. Linear regression models probing statistical predictor of QoL.

		Quality of Life			
Predictor	**Estimate**	**R^2**	**t**	***p*-Value**	**CI**
(Intercept)	116.682		17.852	0.001 *	103.8–129.5
Fatigue	−0.275	0.49	−13.551	0.001 *	−0.31–−0.23
Emotional distress	−0.869	0.59	−9.862	0.001 *	−1.0–−0.69
Illness uncertainty	−0.546	0.60	−3.896	0.001 *	−0.82–−0.27
ECOG	−2.556	0.61	−2.711	0.001 *	−4.4–−0.70
Sex: male	−0.390		−0.360	0.719	−0.13–0.07
Age	−0.027		−0.493	0.622	−2.50–1.40
R^2 adjusted total		0.61			

* These values indicate significance at the 5% level.

4. Discussion

In this study, we have confirmed a high prevalence of fatigue (55.7%) and emotional distress (47.7%) among individuals with advanced, unresectable cancer prior to the start of cancer treatment. Fatigue, emotional distress, and uncertainty about illness were associated with impaired QoL. The clinical variable, ECOG performance status, and the demographic variables of age, sex, and comorbidities also negatively influenced QoL.

Fatigue is widespread among oncological patients, despite the disparity in prevalence rates reported (ranging from 30–99%) [45–50]. In one study carried out in Italy with a sample of 1394 patients with cancer, fatigue was reported in 62% of the cases, severely impacting QoL and, for one of every three patients, hindering their daily activity [51]. This study has examined information from a total of 508 patients from different centers in Spain and determined a 54% fatigue prevalence rate. The Italian series reveals a higher prevalence rate, although it is likely due to how participants were included in the sample and the fact that they were evaluated without regard for disease timing or stage. In this Spanish series, we have examined fatigue among the patients who are going to receive systemic treatment upon diagnosis of an advanced, unresectable disease. In light of the disparate patterns of how different types of cancer evolve, the more protracted survival and follow-up are, the greater the likelihood of fatigue.

We detected no statistically significant differences between patients with fatigue and the same ECOG status based on comorbidities or between locally advanced and metastatic disease in this series. Bearing in mind that the study was conducted prior to initiating antineoplastic treatment, this is probably due to cancer-related immune/inflammatory, metabolic, neuroendocrine, and genetic biomarkers [48] that have an equal effect regardless of the individual's overall status.

Likewise, our series revealed a prevalence of 48% psychological distress, which is more common among women than men (52% vs. 47%) and higher than the 30–50% reported in the literature [25,28,29]. This divergence may be attributable to the sample characteristics (proportion in terms of sex, age, or tumor stage) [52], to the diversity of

instruments used in the studies, and to the timepoint at which our series was evaluated, immediately after diagnosis and just before starting systemic treatment. As with fatigue, these data are not affected by the number or type of comorbidities. Several different studies have shown that being female, together with advanced disease, is one of the greatest risk factors for developing psychological distress, be it in the form of depression or anguish/anxiety [53–56]. In terms of age, despite the fact that elderly people predominate in our sample and country (Spain), we have found more psychological distress in younger participants, as also reported in other series [45].

Our study has shown that fatigue, psychological distress, uncertainty, and ECOG performance status are associated with diminished QoL in people with metastatic cancer prior to initiating systemic treatment. To the best of our knowledge, this is the first study to examine these factors as a whole and their correlation with QoL. Our results indicate that 61% of the variance in QoL can be attributed to these factors. The greater the fatigue, psychological distress, uncertainty, and worse ECOG, the worse the patient's QoL will be. Of all these factors, fatigue accounts for 49% of the decline in QoL, and psychological distress accounts for another 10%.

These results entail compelling clinical implications. As this study evidences, fatigue is one of the most common symptoms among individuals with cancer and can persist for months or even years after treatment [57]. Based on other recent studies, incorporating specific guidelines for physical activity before, during, and after treatment for these patients could decrease fatigue, which, as we have seen here, impairs QoL [58–60]. Through this work, the authors have detected a high prevalence rate of emotional fatigue that several researchers have associated with a reduction in the efficacy of and tolerance to treatment in oncological patients [61]. Consequently, it would be wise to integrate a psychological evaluation into medical oncology consultations and, if necessary, refer the individual to a mental health specialist.

This study has several limitations. The first is that it included patients with different tumor types that we have not been able to compare to each other; consequently, we cannot extrapolate these data to particular types of metastatic neoplasms. The second is that the study was conducted among the Spanish cancer population, and care must be exercised when transferring our results to other countries, especially non-Western countries, inasmuch as cancer care depends on the organization of the country's healthcare system and economy and Spain offers universal access to public healthcare. The third limitation is that, given the cross-sectional design of this study, with patients' being evaluated after diagnosis and before beginning treatment, causality of the associations cannot be inferred, nor can the variability of the prevalence of fatigue and emotional distress over the course of advanced disease be ascertained. Future studies must assess the causal relationship between fatigue, psychological distress, and uncertainty and QoL in individuals with cancer at several timepoints to determine the changes in QoL and what may be causing them.

5. Conclusions

In short, this prospective, multicenter study reveals that there is a high prevalence of fatigue and psychological distress upon diagnosis of advanced, unresectable cancer and that they impact patients' QoL. Similarly, a high prevalence of uncertainty surrounding the disease has been found; nevertheless, we have been unable to demonstrate that this is independently related to decreased QoL. This should prompt oncologists to be more interested in studying and treating the fatigue, emotional distress, and uncertainty surrounding their disease that tend to go unnoticed or are underappreciated.

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Institutional Review Board Statement: The study was approved by the Research Ethics Committee of the Principality of Asturias (17 May 2019) and by the Spanish Agency of Medicines and Medical Devices (AEMPS) (identification code: L34LM-MM2GH-Y925U-RJDHQ). The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study is an observational, non-interventionist trial. Signed informed consent was obtained from all patients.

Informed Consent Statement: Informed consent and approval by the national competent authorities includes permission for publication and diffusion of the data.

Data Availability Statement: The datasets generated during and analyzed during the current study are not publicly available for reasons of privacy. They are however available (fully anonymized) from the corresponding author on reasonable request.

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Mental Adjustment, Functional Status, and Depression in Advanced Cancer Patients

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Abstract: Depressive symptoms are common in individuals with advanced cancer. Objectives. This study sought to analyze the relationship between physical and functional status and depressive symptoms, and to assess the role of mental adjustment across these variables in people with advanced cancer. Methods. A prospective, cross-sectional design was adopted. Data were collected from 748 participants with advanced cancer at 15 tertiary hospitals in Spain. Participants completed self-report measures: Brief Symptom Inventory (BSI), Mini-Mental Adjustment to Cancer (Mini-MAC) scale, and the European Organization for Research and Treatment of Cancer (EORTC) questionnaire. Results. Depression was present in 44.3% of the participants and was more common among women, patients <65 years old, non-partnered, and those with recurrent cancer. Results revealed a negative correlation with functional status, and functional status was negatively associated with depressive symptoms. Mental adjustment affected functional status and depression. Patients having a positive attitude displayed fewer depressive symptoms, while the presence of negative attitudes increased depressive symptoms in this population. Conclusions. Functional status and mental adjustment are key factors in the presence of depressive symptoms among people with advanced cancer. Assessment of functional status and mental adjustment should be considered when planning treatment and rehabilitation in this population.

Keywords: mental adjustment; depression; advanced cancer; health-related quality of life; functional status

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1. Introduction

Patients with advanced cancer often experience varying degrees of depression for a host of reasons, including as a reaction to the cancer diagnosis, symptoms secondary to the tumor itself, treatment, and uncertainty surrounding the risk of disease progression [1–3]. Estimates of the prevalence of depression in individuals with advanced cancer range from 18 to 67% [4–6]. According to Derogatis [7], depression is characterized by feelings of tension, worry, sadness, and irritability perceived by the patient; it is associated with decreased functional status, worse treatment compliance, longer hospitalizations, and a lower survival rate [6,8,9], prompting growing attention on the part of clinicians and researchers.

Several psychosocial factors, including age, sex, type of tumor, and disease progression, can contribute to the development of depression in individuals affected by cancer [10,11].

In a systematic review (40 articles) involving people with cancer, females were more likely to develop depression than males; as for age, most research indicates that younger oncology patients exhibit more depressive symptoms than older ones, but thet results are inconclusive, with some studies reporting the opposite [12]. As for physical factors, people with comorbidities and other chronic conditions were at a higher risk of depression; similarly, a worse cancer stage and metastases were associated with higher rates of depression [12]. In cases of advanced cancer, younger patients and women tended to exhibit more symptoms of depression than men and older individuals [5,13].

Physical and functional status are particularly significant in advanced cancer patients, considering the extent of cancer symptoms, comorbidity with other conditions, the ease with which a person can perform daily activities, and how much help is needed for basic self-care [14,15]. Functional status has long been acknowledged as a predictor of cancer outcome [16,17] and many studies confirm its importance as a predictor of survival in advanced cases [17–19]. People with an impaired functional status tolerate cancer treatments worse [18,20] and experience a poorer course of disease than others with the same stage of cancer [19,20], as well as being at greater risk for suffering mood disorders, such as depression, and decreased quality of life [21,22]. Coping strategies can play a pivotal mediating role between functional status and depressive symptoms.

In recent years, there has been a growing interest in understanding and addressing the challenges associated with coping with cancer. Mental adjustment refers to an individual's cognitive and behavioral reactions to receiving a diagnosis of cancer [23]. Active and positive coping styles in the face of cancer correlate with better adjustment to the disease, treatment adherence, and quality of life, thereby bolstering the patient's sense of self-efficacy and personal control [21,24,25], whereas avoidant coping with cancer, hopelessness, anxious preoccupation, or the presence of negative attitudes increase symptoms of depression in individuals with cancer and cause greater stress and difficulty in undertaking actions relating to managing their condition [26,27].

Identifying factors associated with depression can provide a reference for intervention and treatment. To the best of the authors' knowledge, there are no studies that analyze the role of mental adjustment across physical and functional status and depressive symptoms in a large sample of Spanish patients with advanced cancer. The study objective was to examine the relationship across physical and functional status and depressive symptoms and evaluate the role of mental adjustment on these variables in advanced cancer. The hypothesis is that functional status, mental adjustment, and depression are interconnected, and that mental adjustment (as in negative and positive attitudes) play a significant role in the relationship between functional status and depression.

2. Materials and Methods

2.1. Participants and Procedure

This is a multicenter, prospective, cross-sectional study. Cases of advanced cancer were consecutively recruited from 15 medical oncology departments of different hospitals in Spain between February 2020 and June 2022. Patients were selected at their first visit to the medical oncologist who explained the diagnosis, stage, incurable disease status, and systemic antineoplastic treatment options. Eligible candidates were over 18 years of age with histologically confirmed, advanced cancer who were not eligible for surgery or other therapies with curative intent. Patients with physical conditions, comorbidity, and/or age that represented a contraindication in the opinion of the attending oncologist to receive antineoplastic treatment; who had received cancer treatment in the previous 2 years for another advanced cancer; or with any underlying personal, family and sociological, geographical, and/or medical condition that could hinder the patient's ability to participate in the study were excluded. A total of 857 patients were enrolled; 837 were eligible, and 20 were excluded (6 did not meet the inclusion criteria; 4 met an exclusion criterion, and 10 had incomplete data), as shown in the flow diagram, Figure 1.

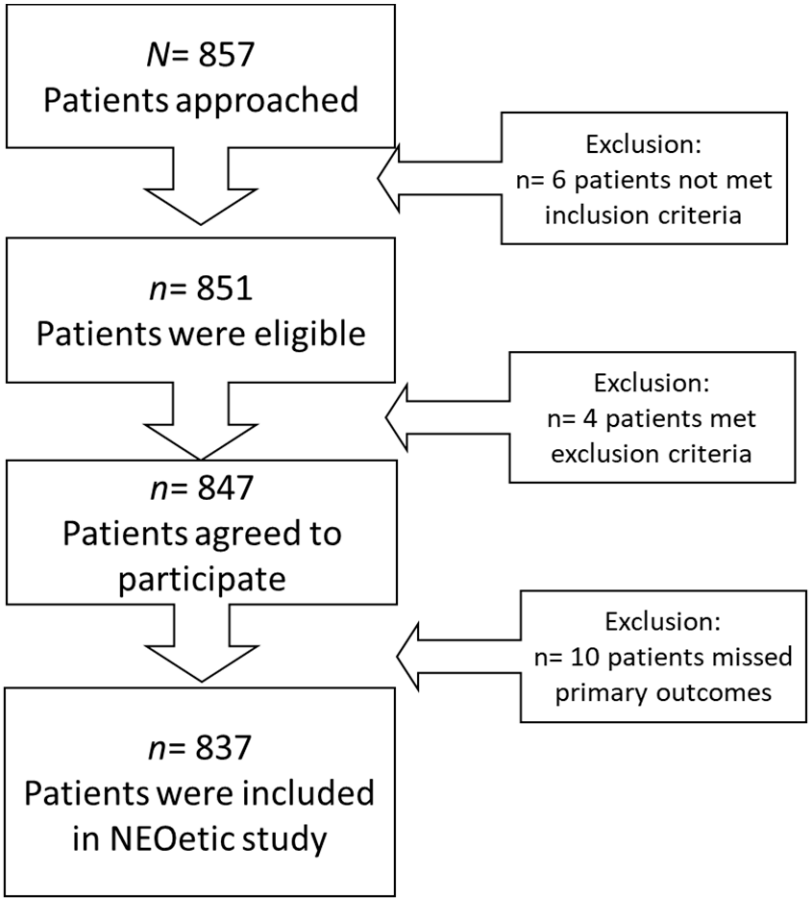

Figure 1. Flow diagram of the NEOetic study.

This research was conducted in accordance with current ethical principles and had the prior approval of the Ethics Review Committees of each institution and of the Spanish Agency of Medicines and Health Products (AEMPS; identification code: ES14042015). The study involved completing several questionnaires and collecting clinical data from the interview and medical history. Data collection procedures were similar in all hospitals and patients' data were obtained from the institutions where they received treatment. Those who agreed to participated signed the consent form, were given instructions on how to fill in the written questionnaires, completed it at home, and handed them to the auxiliary staff at the following visit. All participants provided informed consent before inclusion. Data were collected and updated by the medical oncologist, through a web-based platform (www.neoetic.es).

2.2. Measures

Demographic information, including age, sex, marital status, educational level, and employment status, and questionnaires were provided by the patients in writing. The three questionnaires (Brief Symptom Inventory, Mini-Mental Adjustment to Cancer, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) were completed at home during the interval between the first visit to the oncologist and the beginning of systemic treatment. Clinical variables pertaining to cancer such as primary tumor site, histology, recurrent cancer (yes/no), anti-neoplastic treatment, and outcomes were gathered by the medical oncologist from the medical records.

Depression was assessed using the Brief Symptom Inventory (BSI) [7]. The questionnaire consists of six descriptions of physical and emotional complaints of depression. The depression subscale quantifies symptoms of discontentment, disaffection, and dysphoric mood, e.g., self-deprecation, anhedonia, hopelessness, and suicidal ideation. Each item

is scored on a 5-point Likert scale; the score for each subscale ranges from 0 to 12, with higher scores indicating greater depression. Raw scores are converted to T-scores based on gender-specific normative data. To identify individuals with significant levels of depression, the BSI applies the clinical case-rule. According to the cut-off values recommended by Derogatis [7], patients whose T-score $\geq$ 63 were considered to have "probable depression". The Spanish version of the BSI has proven good reliability and validity in the Spanish population [28].

Coping strategies for cancer were assessed using the Mini-Mental Adjustment to Cancer (Mini-MAC) [23]. It contains 29 items that evaluate three factors: negative attitude (anxious preoccupation and helplessness), positive attitude, and cognitive avoidance. The items are scored on a 4-point Likert scale; the higher score, the more that coping strategy is used. The Spanish version of the Mini-MAC scores had reliability estimates (Cronbach's alpha) ranging from 0.88 to 0.9 [29].

Symptoms and functional status were probed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) [30], comprising 30 items, 24 of which are aggregated into nine multi-item scales: five functioning scales (physical, role, cognitive [CF], emotional, and social); three symptom scales (fatigue, pain, and nausea and/or vomiting), and one global health-status scale. The remaining six single items assess symptoms of dyspnea, appetite loss (AP), sleep disturbance, constipation, diarrhea, and financial impact. Response choices vary from 1 (not at all) to 4 (very much). All scales' scores are linearly transformed to a 0–100 scale. Higher scores indicate better functional status as well as more physical symptoms. Score reliability estimates for the Spanish version were 0.88–0.96 [15].

2.3. Data Analysis

Descriptive statistics were performed and both means (M) and standard deviations (SD) were calculated for demographic and clinical characteristics. ANOVAs were used to examine differences in depressive symptom (BSI score) as a function of demographic and clinical variables. Eta squared (η^2) was computed to assess effect size of continuous variables. Eta-squared ranged from 0 to 1, with η^2~0.01, η^2~0.06, and $\eta^2 > 0.14$ for a small, medium, and large effect size, respectively [31]. Bivariate correlations were used to evaluate the association between symptom and functional scale (EORTC), coping strategies (M-MAC), and depression (BSI). All data were inspected for normality, outliers, and the assumptions of multicollinearity and homoscedasticity [32]. Structural Equation Modeling (SEM) is capable of building, estimating, and testing theoretical models of the relationships between variables. It can substitute multiple regression and other methods to analyze the strength of correlations between individual variable indicators in a specific population [33]. In this study, the previously determined significant factors were used in the SEM to identify the relationship between symptom and functional scale, coping strategies, and depression. Standardized direct, indirect, and total effects with corresponding 95% bias-corrected confidence intervals (CI) were measure using the bootstrapping methods [33,34]. The model fit was tested by means of the normed χ^2 value (NC; desired value < 2.0, desired significance $p < 0.05$), goodness-of-fit index, Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), Normed Fit Index (NFI) (>0.95 indicating an excellent fit), and root mean square of approximation (RMSEA; desired value < 0.06) [33]. Bilateral statistical significance was set at $p < 0.05$ for all tests. Statistical analyses were performed using the IBM-SPSS 23.0 statistical and AMOS 23.0 software package for Windows PC.

3. Results

3.1. Demographics and Clinical Characteristics

Data from 837 participants (mean age, 65 $\pm$ 10.6) were included in the analysis after excluding missing data (n = 10). Most of the participants were men (54%); 78% were married; 52% completed junior high school; and 51% were retired or unemployed. The most common tumors were bronchopulmonary (32%), colorectal (15%), pancreatic (10%), breast (7%), and

gastric (6%). Adenocarcinoma histology was the most prevalent (63%) and most cancers were diagnosed in stage IV (81%). The most frequent treatment was chemotherapy alone or combined with other treatment modalities (80%). Estimated survival was <12 months for 27% of the sample.

Based on the cut-off values, the overall prevalence of depressive symptoms in the study population was 46%. Mean values were 63.4 ± 7.1 for depressive symptoms. One-way ANOVA denoted that there were statistically significant relationships between depressive symptoms and sex (F = 17.685, p = 0.001, partial eta-squared = 0.021), age (F = 2.691, p = 0.030, partial eta-squared = 0.013), marital status (F = 7.881, p = 0.005, partial eta-squared = 0.012), and recurrent cancer (F = 6.540, p = 0.011, partial eta-squared = 0.008); no significant differences were found for the remaining variables (see Table 1). Using a cut-off point < 75 [35] to identify people with functional problems, 41% of the participants indicated that they had difficulties in carrying out activities of daily living.

Table 1. Baseline characteristics (n = 837).

Variables		n (%)
Age (M; SD)	65.2 ± 10.6	
Sex	Male	454 (54)
	Female	383 (46)
Marital status	Married or partnered	653 (78)
	No partnered	174 (22)
Educational level	≤Primary school	405 (48)
	≥High school	432 (52)
Employment	No employ	422 (51)
	Employ	415 (49)
Primary tumor site	Broncho-pulmonary	266 (32)
	Colon	122 (15)
	Pancreas	83 (10)
	Breast	62 (7)
	Stomach	47 (6)
	Others	257 (31)
Histology	Adenocarcinoma	526 (63)
	Others	311 (37)
Recurrent cancer	Yes	677 (19)
	No	160 (81)
Stage	Locally advanced	161 (19)
	IV	676 (81)
Oncology treatment	Chemotherapy	670 (80)
	Others	167 (20)
Time-estimated patient survival	<12 months	224 (27)
	>12.1 months	613 (73)

Abbreviations: M, Mean; SD, Standard Deviation.

3.2. Correlations across Variables

Depressive symptoms correlated positively with sex (r = 0.144, p < 0.001), marital status (r = 0.108, p = 0.005), symptom scale score (r = 0.476, p < 0.001), and negative attitude (r = 0.534, p < 0.001), whereas they correlated negatively with age (r = −0.081, p = 0.020), functional scale (r = −0.618, p < 0.001), and positive emotion (r = −0.298, p < 0.001). No significant correlations were detected between cognitive avoidance and depressive symptoms (See Table 2).

Table 2. Correlations across depressive symptoms and study variables.

Variables	Depression	Age	Sex	Marital	Symptom Scale	Functional Scale	Negative Attitude	Positive Emotion	Cognitive Avoid.
Depression	1								
Age	−0.081 *	1							
Sex	0.144 **	−0.068 *	1						
Marital status	0.108 **	−0.182 **	0.126 **	1					
Symptom scale	0.476 **	−0.104 **	0.139 **	0.127 **	1				
Functional scale	−0.618 **	0.063	−0.179 **	−0.090 *	−0.764 **	1			
Negative attitude	0.534 **	0.071 *	0.051	0.037	0.298 **	−0.419 **	1		
Positive emotion	−0.298 **	−0.100 **	−0.093 **	0.014	−0.116 **	0.215 **	−0.174 **	1	
Cognitive avoid.	0.064	−0.048	−0.039	0.036	0.052	−0.043	0.277 **	0.447 **	1

* $p < 0.05$; ** $p < 0.01$. Age as a continuous variable; Sex: 0 = Male, 1 = Female; Marital Status: 0 = Married or partnered, 1 = Not partnered.

3.3. Relationship across Symptom and Functional Scale Scores, Coping Strategies, and Depression: Path Analysis

The model exhibited excellent fit to the data ($\chi 2 = 14.718$; $p = 0.005$; CFI = 0.993; NFI = 0.990; TLI = 0.982; RMSEA = 0.057 (90% CI = [0.028, 0.089]). As displayed in Figure 2, the symptom was directly and negatively associated with functional scale score ($\beta = -0.76$, $p < 0.01$); functional scale score was directly and positively associated with positive attitude ($\beta = 0.22$, $p < 0.01$), and negatively associated with negative attitude ($\beta = -0.42$, $p < 0.01$) and depression ($\beta = -0.46$, $p < 0.01$). Negative attitude was positively associated with depression ($\beta = 0.32$, $p < 0.01$) and positive attitude was negatively associated with depression ($\beta = -0.15$, $p < 0.01$); the more symptoms patients exhibit, the worse their functional status and the more depressive symptoms increase; furthermore, positive attitude and negative attitude mediated in the association between functional status and depressive symptoms—Figure 2.

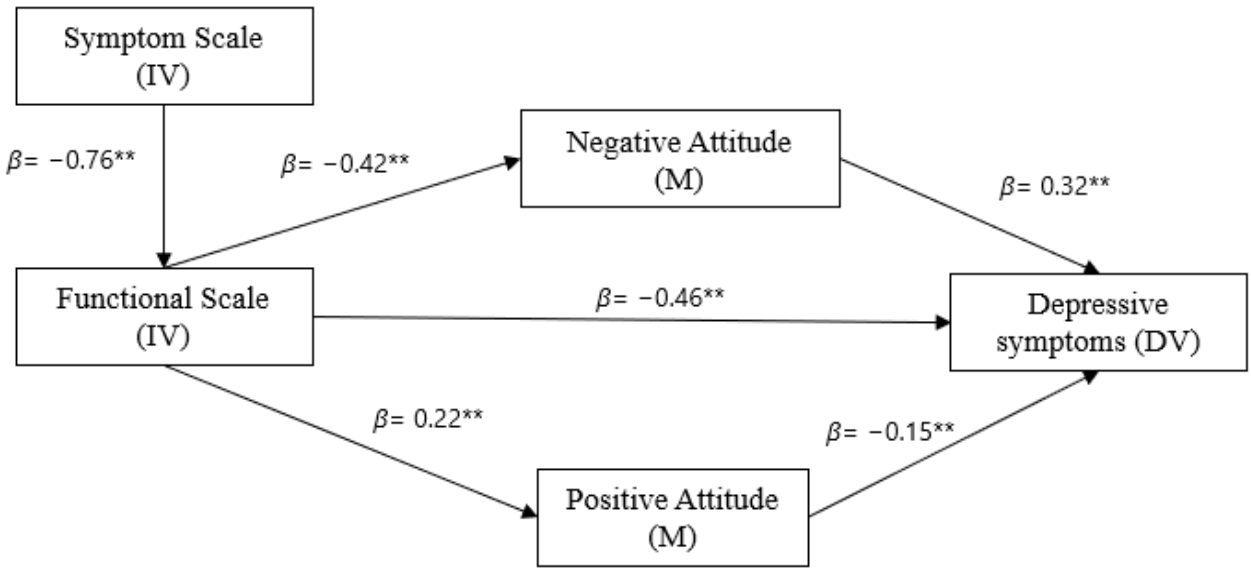

Figure 2. Predictive model of depressive symptoms among patients with advanced cancer. Lines present the significant pathways. ** $p < 0.001$.

4. Discussion

This is the first study to analyze the relationship between physical and functional status, mental adjustment, and depression in a Spanish sample of individuals with advanced cancer. Physical and functional status often correlate with depression in oncological patients [8,36]. The prevalence of the symptoms of depression in this sample was 44.3%, slightly higher than Spanish patients with resected cancer (36.6%) [37], and greater than

the sample of the general Spanish population (4.7%) [38]. This study suggests depressive symptoms are very high among people with cancer, particularly in those with metastasis.

Social factors can also play an important role in patients' emotional state [36,39]. In these series, females, younger individuals, unmarried or unpartnered people, and those with recurrent cancer displayed more symptoms of depression than males, older, married patients, and those suffering from cancer for the first time, which was consistent with the literature [5,12,13]. It would be necessary for healthcare professionals to develop and implement effective measures aimed at assessing and mitigating depressive symptoms in cases of advanced cancer, thereby improving their mental health, given the high rates of depression in advanced cancer patients.

Individuals with advanced cancer generally experience a variety of symptoms, impaired functional status, and the possibility of death [36,40,41]. In this study population, we have found that physical symptoms correlated negatively with functional status, in line with earlier findings [17,42]. Patients with advanced cancer comprise a population at particular risk, given the increase in physical symptoms and impaired functional status, which negatively impacts their psychological health and quality of life [21,22]. In the present study, 41% of the participants indicated that they had a hard time performing activities of daily living [43]. In keeping with a systematic review (n = 43 studies), between 36.7% and 54.6% of cancer sufferers report difficulties in carrying out basic, fundamental activities of daily living [43], which deteriorate further over time [44]. Functional impairment is significantly associated with longer hospital stays and worse survival [17,42]. Patients with a high risk of functional impairment may benefit from services such as home healthcare following discharge, rehabilitation, inpatient exercise programs, home hospitalization, and psychological care. These interventions can help improve the symptoms and functional status of patients [45–47].

The different coping strategies patients use to confront a scenario of functional decline yield disparate results [22,48]. How people with cancer cope is an important resource for psychological adjustment that can ease their stress and psychological distress [49,50]. Functional status was found to be associated with mental adjustment and with depressive symptoms in this study [17,44]. Negative attitudes correlated positively with depressive symptoms, while positive attitude exhibited a negative association with symptoms of depression in patients with advanced cancer. Individuals who display a positive attitude toward the disease that helps them to maintain their trust in adapting to the situation exhibited better mood, whereas those with high levels of negative attitudes, such as preoccupation, anxiety, and hopelessness, suffered more symptoms of depression [51]. The presence of negative attitudes and a declined functional state worsen the symptoms of depression. The positive correlation between negative attitude and depression is compatible with the findings of earlier studies [36,52,53], as well as with a greater sensitivity to pain [54] and shorter survival [55]. One possible explanation is that these individuals may adopt more passive behavior by not keeping follow-up appointments or ignoring symptoms of relapse [53].

4.1. Implications for Clinical Practice and Research

These findings have both theoretical and practical repercussions in healthcare in cases of advanced cancer. The results confirm those previously demonstrated in different cancer populations as regards the relationship between physical and functional status, mental adjustment, and depression. In practice, these data point to patients with advanced cancer as being at risk for presenting impaired functional and emotional status and that coping strategies can lessen said relationship. Mental adjustment evaluations should be contemplated when planning and treating advanced cancer. A more active, positive coping strategy can help patients better confront the challenges posed by the disease. For instance, the study by Trusson and Pilnick suggests that peer support can benefit these individuals and provide them with the chance to express their negative attitudes and concerns [56]; likewise, they can receive practical advice about self-care and improving their emotional state in these groups [56]. Therefore, the clinician should be more aware of this relationship

between functional status and depression in this population, as it appears in other series of older adults with cancer in the Spanish population [57,58].

4.2. Limitations

This study has a series of strengths and limitations. Its greatest strength is that it examines a large population of people with advanced cancer from 15 oncology departments across a wide geographic region in Spain. Nevertheless, several limitations must be considered when interpreting the results. First, all the participants took part in the study voluntarily, which may have introduced a self-selection bias. Second, the study examined the relations between functional status, mental adjustment, and depressive symptoms, as well as analyzing differences in demographic and basic clinical variables. Other factors associated with depressive symptoms must also be probed in future research. Third, this is a transversal study; consequently, a longitudinal study would be worth undertaking to increase the power of the findings.

5. Conclusions

In these series, depression was distinctly prevalent among the participants with advanced cancer. The result of this study substantiates that the patients who present a worse functional status perceive the disease as a source of uncontrolled stress with the presence of feelings of hopelessness, anxious preoccupation, anguish, and discouragement (negative attitude). They experience every change as a sign that their situation is deteriorating, resulting in them feeling worse and experiencing more depressive symptoms. In contrast, those having a more active and positive coping style, attempting to manage their situation, searching for alternatives and solutions, and maintaining their expectations as well as their confidence in being able to adapt to the challenges of the disease (positive attitude) present fewer symptoms of depression. Interventions that seek to enhance functional status and coping strategies could, ultimately, lessen symptoms of depression.

Author Contributions: A.R.-G., C.C. and P.J.-F. developed the project, analyzed the data, and drafted the manuscript. The other authors recruited patients and provided clinical information, comments, and improvements to the manuscript. All authors participated in the interpretation and discussion of data, and the critical review of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was approved by the Research Ethics Committee of the Principality of Asturias (17 May 2019) and by the Spanish Agency of Medicines and Medical Devices (AEMPS) (identification code: L34LM-MM2GH-Y925U-RJDHQ). The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study is an observational, non-interventionist trial. Signed informed consent was obtained from all patients.

Informed Consent Statement: Informed consent and approval by the national competent authorities include permission for the publication and diffusion of the data.

Data Availability Statement: The datasets generated during and analyzed during the current study are not publicly available for reasons of privacy. They are however available (fully anonymized) from the corresponding author upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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Original Article

Can Oncologists Prompt Patient Prognostic Awareness to Enhance Decision-Making? Data From the Neoetic Study

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Abstract

Introduction: Anti-neoplastic therapy improves the prognosis for advanced cancer, albeit it is not curative. An ethical dilemma that often arises during patients' first appointment with the oncologist is to give them only the prognostic information they can tolerate, even at the cost of compromising preference-based decision-making, versus giving them full information to force prompt prognostic awareness, at the risk of causing psychological harm.

Methods: We recruited 550 participants with advanced cancer. After the appointment, patients and clinicians completed several questionnaires about preferences, expectations, prognostic awareness, hope, psychological symptoms, and other treatment-related aspects. The aim was to characterize the prevalence, explanatory factors, and consequences of inaccurate prognostic awareness and interest in therapy.

Results: Inaccurate prognostic awareness affected 74%, conditioned by the administration of vague information without alluding to death (odds ratio [OR] 2.54; 95% CI, 1.47-4.37, adjusted $P = .006$). A full 68% agreed to low-efficacy therapies. Ethical and psychological factors oriented first-line decision-making, in a trade-off in which some lose quality of life and mood, for others to gain autonomy. Imprecise prognostic awareness was associated with greater interest in low-efficacy treatments (OR 2.27; 95% CI, 1.31-3.84; adjusted $P = .017$), whereas realistic understanding increased anxiety (OR 1.63; 95% CI, 1.01-2.65; adjusted $P = 0.038$), depression (OR 1.96; 95% CI, 1.23-3.11; adjusted $P = .020$), and diminished quality of life (OR 0.47; 95% CI, 0.29-0.75; adjusted $P = .011$).

Conclusion: In the age of immunotherapy and targeted therapies, many appear not to understand that antineoplastic therapy is not curative. Within the mix of inputs that comprise inaccurate prognostic awareness, many psychosocial factors are as relevant as the physicians' disclosure of information. Thus, the desire for better decision-making can actually harm the patient.

Keywords: decision-making; information; prognostic awareness; depression; quality of life.

Implications for Practice

This study is the first to evaluate the impact of cancer prognostic awareness on interest in low-efficacy therapies for advanced, unresectable tumors during the initial consultation. Results indicate that inaccurate prognostic awareness remains prevalent in the era of immunotherapy and targeted therapies, affecting decision-making, mood, and quality of life. Oncologists' common ambiguous communication style often fails to address the topic of death. The study highlights the complex interplay of factors that influence the belief in curability and interest in low-efficacy therapies when making treatment decisions. The results of this research also illustrate the ethical and psychological considerations that guide decision-making and the trade-off between autonomy and quality of life, mood, and other factors. The desire for better decision-making may ultimately harm the patient.

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Introduction

Any appointment with the oncologist necessarily entails an ethical dilemma. The problem is that patient-centered decision-making requires that expectations and preferences be aligned with scientific evidence.[1,2] However, many hurdles must be overcome in this situation. To begin with, prognostic awareness is a multifactorial phenomenon in which cultural considerations and individual circumstances are intertwined.[3] In this process, family or physician collusion is not uncommon. Consequently, many subjects with incurable diseases such as cancer, report unrealistic expectations, and misconceptions regarding treatment objectives and are incapable of distinguishing whether the aim is to cure or prolong overall survival (OS).[4-11] This phenomenon can be found in all societies and has even found its way into mainstream culture.[11,12] For instance, in the Cancer Care Outcomes Research and Surveillance (CanCORS) study, 69% and 81% of patients with metastatic lung and colon cancer, respectively, responded in a way that was compatible with the belief in curability.[5] The authors concluded that the misunderstanding surrounding prognosis stood in the way of making preference-based decisions, which in extreme cases, would affect the validity of the informed consent.[13,14] One potential interpretation would be that achieving realistic perceptions about the drugs could theoretically decrease the use of services that would probably not enhance quality of life (QoL) and not dramatically change survival.[1,15] The problem is that conveying something so sensitive as a death sentence takes time, given that it will necessarily trigger psychological suffering and compromise QoL.[8,16,17] Thus, when surveyed, most respond that they want truthful information that will enable them to engage in decision-making, yet at the same time, they need to hold onto hope, and deem abrupt information as lacking compassion.[5,18] Pragmatically speaking, this means that information cannot be forced precisely at a time when it is needed to decide on first-line treatment; hence, the timing for full disclosure has to be pondered. This deliberation must be brief, if treatment efficacy is to remain unaffected. Nonetheless, developing adaptive coping strategies tends to take time; therefore, providing more complete information will either delay treatment[19] or have consequences for the patient's mental wellbeing.

Moreover, the elevated toxicity and scant efficacy of the traditional chemotherapy regimens developed in the 1990s led to the thought that, had they known their prognosis better, some patients would not have accepted treatment.[5] This panorama has changed as a result of the identification of druggable molecular alterations in oncogenes and the development of immune-based therapies, such as immune checkpoint inhibitors.[20,21] Since the palliation/toxicity trade-off is more favorable in some cases, we have used the NEOetic study of the Bioethics Group of the Spanish Society of Medical Oncology (SEOM) to analyze how disclosure of prognostic information and expectations regarding the efficacy of classic (chemotherapy) and modern (immunotherapy and biologics) anticancer drugs for unresectable advanced cancers affect general interest in first-line treatments and psychological outcomes.

Methods

Design and Population

NEOetic is a prospective, multicenter (15 oncology departments) study of the SEOM Bioethics group. The study enrolled patients ≥18 years with advanced or metastatic cancer deemed ineligible for curative resection. These patients were suitable candidates for systemic cancer treatment, as determined by the oncologist during their initial visit. The eligibility criteria did not entirely rule out the potential for some patients to be considered for resection after a positive response to systemic treatment or achieving long-term survival with immunotherapy. Exclusion criteria consisted of subjects not eligible for systemic, antineoplastic treatment or who, in the oncologist's opinion, were not suitable to participate, as well as those who had received cancer treatment in the last 2 years. Those who agreed to take part signed the informed consent form, were instructed on how to fill in the printed questionnaires, which they completed at home and handed in to the auxiliary personnel prior to initiating systemic treatment. The study was approved by the Ethics Committee of each participating center and was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

Study Measures

Clinical data were gathered by the oncologist during the patient interview and clinical history prior to initiating therapy and was similar at all participating centers. Participants completed a questionnaire regarding demographic characteristics, including aspects such as education, family and social structure, employment status, and clinical data.

The psychometric questionnaires used were: Mini-MAC (Mini-Mental Adjustment to Cancer Scale),[22] EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life C30 Questionnaire),[23,24] BSI-18 (Brief Symptom Inventory 18),[25,26] FACIT-Sp-12 (Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale),[27,28] HHS (Herth Hope Scale),[29,30] Duke-UNC-11 (perceived social support),[31,32] MUIS-C (Mishel Uncertainty in Illness Scale-Community form),[33] SWD (Satisfaction With Decision),[34] CWQ-FoR (Cancer Worry Questionnaire),[35] NEOetic-EIT (expectations regarding treatment effectiveness), NEOetic-POI (Preference On Information), and NEOetic-IIT (Interest In therapy), STAR-P (Scale to Assess the Therapeutic Relationship-Patients' version).[36] The characteristics, interpretation, and validation in Spanish of these questionnaires can be found in Supplementary Table S1.

The NEOetic-EIT scale was created specifically for this study and was tested on the first 30 participants, at which point the decision was made to continue without any modification. The "belief in curability of the cancer" variable was obtained from the question: "Do you think the treatment will help cure your cancer?." Accurate prognostic awareness was defined as disagreeing or strongly disagreeing [with the belief] that their cancer could be cured.

NEOetic-IIT quantified the potential interest in treatment by means of 6 items that represented scenarios with hypothetical therapies with successively greater OS benefits, lacking other alternatives. For this study, low-efficacy therapy was considered to be the one that prolonged OS by less than 6 months. The subject was considered to be interested when the rating was "likely" or "very likely."

Statistics

Proportional odds (PO) regressions were fitted to model the endpoints. Predictors were chosen theoretically, following consensus among the project coordinators and systematic review of the literature. The qualitative judgment of several

studies with consistency criteria, theoretical plausibility, causality, and lack of temporal ambiguity was considered. Redundancy analyses were conducted via flexible parametric additive models to rule out the possibility of some model variables being predicted by the remaining covariates.[37] The limiting sample size supports a model having a maximum of 30 coefficients.[37,38] Brant's tests and a likelihood ratio tests were applied to evaluate the PO assumption.[39,40] This assumption was fulfilled in all the models. The existence of interactions was explored systematically, creating interaction terms such as "belief in curability of the cancer" × "coping strategy."[8] In the event that significant interaction terms ($P < .05$) were found, subgroup analyses were performed. In addition, the non-linearity of all the continuous variables was probed using natural splines when necessary. The CIs of the model predictions were adjusted to the average or reference value of the covariates. Other exploratory analyses were conducted with Kendall's Tau rank correlations or χ2-tests for proportions. Adjusted *P*-values were calculated by the Bonferroni-Holm (BH) method with $\alpha = .05$. Missing values were minimized during the monitoring of the study and only affected 5 cases (<1%), applying complete case analysis. Analyses were performed using R v4.05 including the rms library.[41] Examples of the R code are presented in Supplementary Table S2.

Results

Patients

The database contains 550 patients with unresectable advanced cancer (incurable) recruited over the course of 2 years (2020 and 2021); baseline characteristics are summarized in Table 1. Information on belief in curability was available for 545 of them (see flow diagram in Supplementary Fig. S1). Most were male (58%, *n* = 319) with a median age of 66 years (range, 18-90). Almost one quarter (24%, *n* = 133) were over the age of 70. The most commonly cancers were bronchopulmonary (37%, *n* = 203), colorectal (22%, *n* = 123), and other digestive neoplasms (22%, *n* = 122). Regarding therapies, 21% (*n* = 117) received immunotherapy, while 23% (*n* = 126) were given targeted therapy with or without chemotherapy. Only 1 patient (0.2%) declined systemic treatment after the initial consultation with the oncologist, while 16 patients (2.9%) opted for antineoplastic therapy following a second opinion at a different center.

The participants displayed great concern for their health; 51% (*n* = 282) were afraid of dying and 84% stated that they were aware of the severity of their disease. Nevertheless, most (74%, 407/550) agreed that the treatment would help to cure their cancer. Only 17.6% (95% CI, 14.6-21.0) were clearly cognizant of their prognosis. In contrast, the oncologist estimated the median OS to be 22.6 months (range, 5-100) for the entire group, and physicians agreed that long-term survival was possible in only 13.4% (*n* = 74).

The most common communication style was qualitative without alluding directly to demise (65%, *n* = 356). Of the ones who conveyed quantitative information, 38% (24/63) reported relative data, 49% (31/63) absolute outcomes, 6% (4/63) showed the participant the pivotal trial, and in the rest, it was unclear (Fig. 1). Indices of satisfaction with the interview and doctor-patient relationship were high (see questionnaire in Supplementary Table S1).

Table 1. Baseline characteristics.

	N (%)
Age, median (range)	66 (18-90)
Sex, female	231 (42)
Tumor	
Colorectal	123 (22.3)
Lung	203 (36.9)
Head and neck	16 (2.9)
Upper GI	122 (22.1)
Breast	29 (5.2)
Others	57 (10.3)
ECOG PS	
0	189 (34.3)
1	325 (59.0)
≥2	36 (6.5)
Oncological setting	
Unresectable metastases	401 (72.9)
Potentially resectable metastases	41 (7.4)
Resectable early metastases	8 (1.4)
Locally advanced unresectable	89 (16.1)
Locally advanced potentially resectable	11 (2.0)
Therapy	
Immuno-therapy	117 (21.3)
Chemotherapy	306 (55.6)
Targeted therapy	126 (22.9)
The patient declined to receive systemic treatment	1 (0.2)
QLQ-C30 symptoms scale, median (range)	27.1 (0-94.4)
Administered information profile	
Not informed because of conspiracy	3 (0.55)
Not reported as inappropriate	7 (1.27)
Qualitative information without alluding to death	356 (64.7)
Qualitative information alluding to death	121 (22.0)
Approximate quantitative information	51 (9.2)
Accurate quantitative information	12 (2.1)
Marital status	
Married or in a couple	374 (68.0)
Single	62 (11.2)
Divorced	63 (11.4)
Widowed	51 (9.2)
Number of children	
0	83 (15.0)
1	104 (18.9)
2	227 (41.2)
≥3	136 (24.7)
Education level	
No education	49 (8.9)
Primary education	217 (39.4)
Secondary education	153 (27.8)
University studies	131 (23.8)
Employment status	
Not working	2 (0.3)
Retired	248 (45.0)
Part-time worker	1 (0.1)
Full-time worker	299 (54.3)

Table 1. Continued

	N (%)
Primary caregiver	
Alone, no support	39 (7.0)
Family	498 (90.5)
Friend/ acquaintance	9 (1.6)
Staff of an institution (residence)	4 (0.7)

Abbreviations: ECOG PS, Eastern Cooperative Group performance status; upper GI, upper gastrointestinal tumor; QLQ, quality of life questionnaire.

Predictors of Inaccurate Prognostic Awareness

After noting that inaccurate prognostic awareness was prevalent (Fig. 1), we wanted to assess the associated factors. In the ordinal multivariable model, the most common administered information profile (qualitative information without alluding to death) augmented inaccurate prognostic awareness, versus the disclosure of quantitative information (approximate or precise) (odds ratio [OR], 2.54; 95% CI, 1.47-4.37; adjusted P = .006). In absolute terms, this entailed a belief in curability in 67.9% (95% CI, 49.5-82.1) vs. 79.9% (95% CI, 47.7-94.5) among patients who received full disclosure compared to uninformed subjects, respectively. Vague information making no reference to death and no information had the same explanatory effect. In a sensitivity analysis, quantitative information was effective when it was communicated as absolute risk reductions (OR 0.37, 95% CI, 0.19-0.70), but not when relative effect measures were provided (Supplementary Table S3). Moreover, other factors associated with increasing belief in curability were hope, spirituality, fighting spirit, tumor site other than breast, prolonged expected survival time (with a threshold of around 20 months), and not being afraid to die (Table 2; Supplementary Table S4). The marginal effects are shown in Fig. 2.

Predictors of Interest in Low-Efficacy Therapies

The survey concerning preferences detected that 68% (378/550) agreed to low-efficacy therapies, which was greater in participants with inaccurate prognostic awareness. To probe further into this phenomenon, we fitted an ordinal multivariable model with an interest in low-efficacy therapies as the response variable. Accurate prognostic awareness correlated with less interest in low-efficacy treatment. Thus, this interest rate was 56.3% (95% CI, 38.5-72.7) and 74.2% (95% CI, 61.2-83.9) among subjects with an accurate prognostic awareness compared to those who stated that cure was "very likely" (OR 0.44; 95% CI, 0.26-0.76; adjusted P = .017). Other factors associated with more interest in low-efficacy therapies were greater perceived social support and greater hope (Fig. 3; Supplementary Fig. S2).

Correlation Between Prognostic Awareness and Other Endpoints

Believing in cure correlated with several endpoints, such as greater fighting spirit, fatalism/stoic acceptance, hope, global health status, and satisfaction with decision and care (Fig. 4). In contrast, the belief in curability negatively correlated with uncertainty, helplessness/hopelessness, depression, anxiety, somatization, and several symptoms (Supplementary Fig. S3).

To delve further into the impact of prognostic awareness, we fitted multivariable models for QoL, depression, and anxiety (details and specifications can be found in Supplementary Table S5). A higher BSI-anxiety score was observed in individuals who did not believe in the curability of cancer (OR 1.63; 95% CI, 1.01-2.65; adjusted P = .038), with evidence of an interaction with coping based on fighting spirit (P-value [interaction] = .0199) (Supplementary Fig. S4).

The predicted mean BSI score for depression was 70.8 (95% CI, 67.5-73.1) and 67.8 (95% CI, 64.5-70.1) among participants with an accurate prognostic awareness vs. those who deemed curability as being "very likely" (OR, 1.96; 95% CI, 1.23-3.11; adjusted P = .020). Mood was found to be correlated with other factors such as fear of dying, being male, having symptoms, or lack of social support (Supplementary Table S5). The predicted mean QLQ-C30—Global health status was 47.8 (95% CI, 37.0-56.8) and 57.7 (95% CI, 49.7-65.2) in individuals who had an accurate prognostic awareness compared to those who believed that curability was "very likely" (OR, 0.47; 95% CI, 0.29-0.75; adjusted P = .011). The correlations between the interest in low efficacy therapies and other endpoints are shown in Supplementary Table S6.

Discussion

In the course of this study, we have found that, following their first appointment with the oncologist, only 18% of the individuals with incurable cancer understand that the antineoplastic therapy is not curative. While repeated discussions with the oncologist throughout the patient journey may lead to a better understanding of prognosis over time, patients may not be fully aware of the true benefits of therapies during the initial visit when therapeutic decisions must be made. This finding is perplexing, especially considering the widespread information and awareness surrounding cancer in modern society. Nevertheless, the percentage is only slightly lower than that of the CanCORS study, with the same measurement instrument,[5] albeit appreciably lower than studies from 2 or 3 decades ago in multiple cultural contexts.[11] The persistent nature of these findings despite the progress made in oncology, suggests the need for further research to uncover the underlying reasons, and to enhance communication between patients and oncologists for better-informed treatment decisions.

In our study, the oncologist's most common prognostic disclosure (~65%) was qualitative, without so much as the mere mention of death. This ambiguous profile worsened prognostic awareness by 12 percentage points, in contrast to the quantitative disclosure expressed in the form of absolute risks and with some explicit allusion to demise. Nevertheless, more complete disclosure did not keep approximately 2/3 of the well-informed participants from expressing unrealistic expectations, which points toward more complex underlying causes. Some such aspects include spirituality, fighting spirit, or constructs that interject emotional components that contribute to the person believing in the possibility of being cured, regardless of the scientific data.[42-44]

The most notorious consequence of the lack of prognostic awareness is the 18% increase in interest in therapies having low efficacy. It is difficult to check this datum against the rest of the bibliography, as most of the series are from the field of

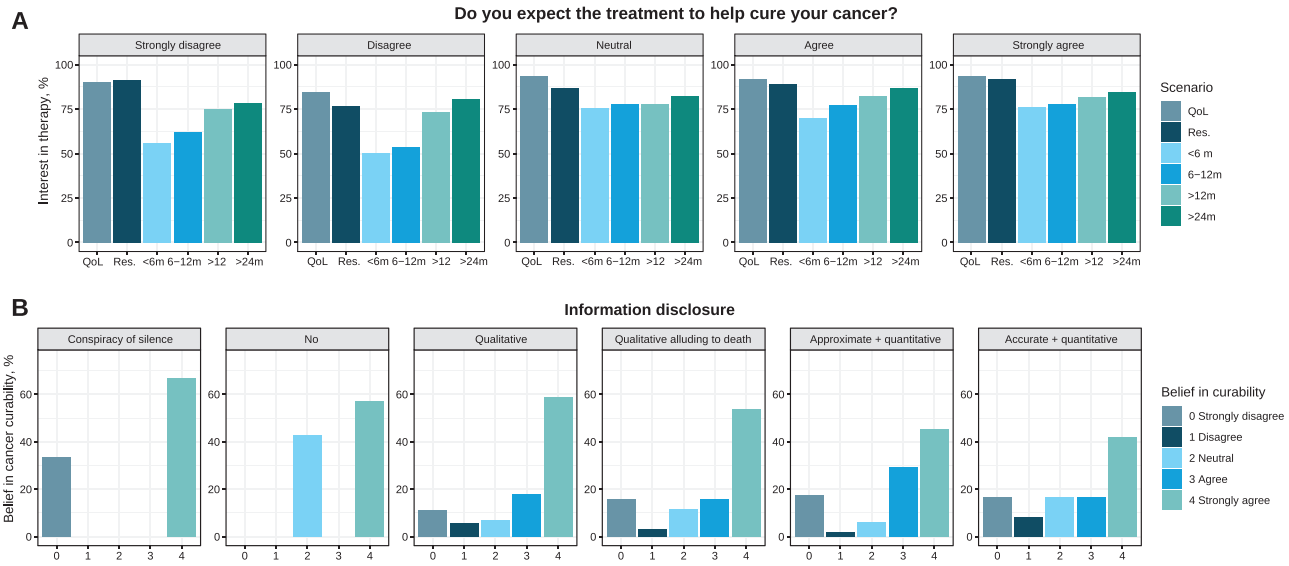

Figure 1. (**A**) Relationship between belief in curability vs. interest in therapy. (**B**) Relationship between type of disclosure and belief in curability. Abbreviations: QoL, quality of life; Res, treatment that achieves tumor response; <6m, treatment that increases survival by at least 6 months; 6-12m, treatment that increases survival by between 6 and 12 months; >12m, treatment that prolongs survival by more than 12 months, >24m, treatment that increases survival by more than 24 months. Note: (A) Displays the percentage of individuals interested in antineoplastic therapy under different assumptions regarding its efficacy (symptom relief or improvement in quality of life only, antitumor response without prolonging survival, or survival increments <6, 6-12, >12, or >24 months). Each panel represents possible responses to the question: "Do you expect the treatment to help cure your cancer?." Each panel in (B) represents a different communication style of the oncologist, with the bars showing whether the patient agreed with the belief that their cancer could be cured.

Table 2. Proportional odds regression for "belief in curability of the cancer."

Effects	OR (95%, CI)
Age, 72 vs. 59	0.92 (0.72-1.18)
Expected survival, 25 vs. 12 months	1.78 (1.10-2.86)
QLQ-C30 symptoms scales, 43 vs 15	0.82 (0.63-1.06)
Spirituality (FACIT), 23 vs. 8	1.24 (1.00-1.55)
Children, 2 vs. 1	1.01 (0.87-1.17)
Perceived social support (Duke-UNC-11), 48 vs. 39	1.38 (0.95-2.02)
Hope (Herth scale), 14 vs. 11	1.60 (1.22-2.09)
ECOG PS >1	0.99 (0.48-2.06)
Fighting spirit (mini-MAC), 100 vs. 67	3.00 (1.77-5.08)
Sex, female	0.73 (0.49-1.08)
Oncological setting, potentially resectable vs. unresectable metastases	1.64 (0.80-3.36)
Oncological setting, locally advanced vs. unresectable metastases	1.43 (0.87-2.34)
Immuno-therapy vs. chemotherapy	0.95 (0.55-1.63)
Targeted therapy vs. chemotherapy	0.80 (0.48-1.32)
Education, no vs. primary education	0.54 (0.28-1.02)
Education, secondary vs. primary	0.79 (0.50-1.24)
Education, university studies vs. primary education	0.87 (0.54-1.40)
Fear of death, none vs. severe	2.29 (1.44-3.65)
Fear of death, moderate vs. severe	1.29 (0.83-2.01)
Colorectal vs. lung cancer	0.87 (0.47-1.61)
H&N vs. lung cancer	0.60 (0.20-1.79)
Upper GI vs. lung cancer	0.70 (0.40-1.22)
Breast vs. lung cancer	0.16 (0.68-0.41)
Other tumors vs. lung cancer	0.76 (0.38-1.51)
Information disclosure, non vs. qualitative (death not mentioned)	0.73 (0.18-2.91)
Information disclosure, qualitative, death alluded vs. qualitative (death not mentioned)	0.73 (0.47-1.15)
Information disclosure, quantitative vs. qualitative (death not mentioned)	0.39 (0.22-0.67)

Odds ratios >1 denote greater belief in curability.

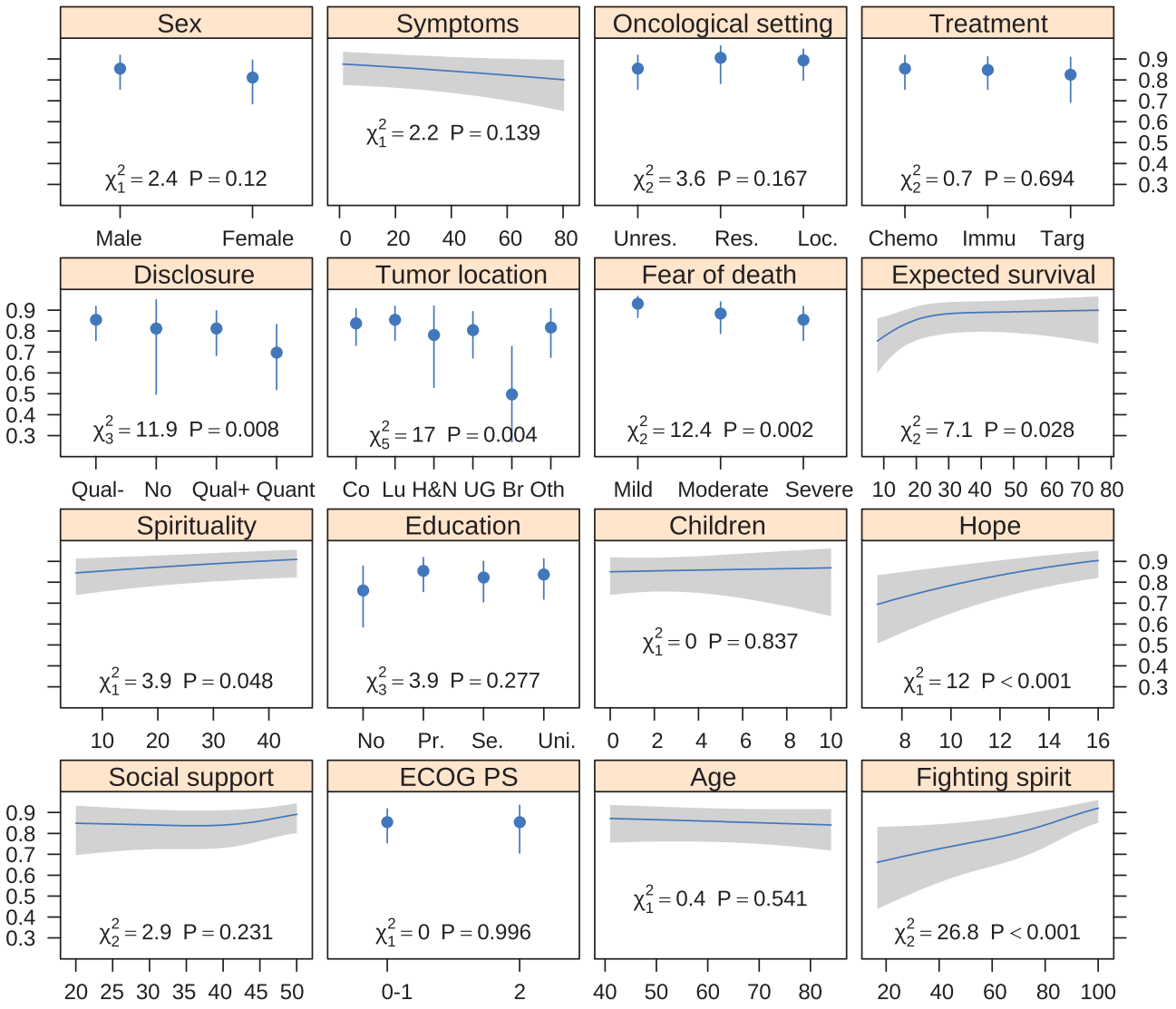

Figure 2. Marginal effects for the model of belief in curability. For each variable, the plot shows the probability that the belief that cancer can be cured is scored as likely or very likely. All other covariates are held constant at the average or baseline level. The main assumptions of the model are shown. Wald tests for the most meaningful hypotheses in a design are shown. Abbreviations: Br, breast cancer; chemo, chemotherapy; co, colorectal; H&N, head and neck cancer; immu, immunotherapy; lu, lung cancer; oth, other tumors; Pr, primary eductation; qual– , qualitative, death not alluded; qual + , qualitative, death alluded; quant , quantitative; Se, secondary education; targ, targeted therapies; UG , upper gastrointestinal cancer; uni, university studies.

adjuvancy, where the aim is to cure, or from the context of palliative care in terminal or refractory patients.[45-47] At present, there is a hefty body of evidence that upholds the observations that the preferences in both scenarios are conflicting, with well-informed subjects who weigh the possibility of suffering side effects differently on the basis of whether or not there is a chance to be cured.[1,2,15] Specific first-line data are scarce.

Overall, our data provide a nuanced confirmation of an idea outlined in the CanCORS study, as well as other authors findings,[5,46,47] according to which, inaccurate prognostic awareness would compromise the ability to make informed decisions. This conclusion requires that certain caveats be taken into account. To begin with, although the degree of prognostic awareness was the single trait most strongly associated with interest in low-efficacy therapies, the combination of other factors such as hope and social support consistently predicted interest in such therapies, even more so than the degree of prognostic disclosure. Second, regardless of individual realism, most of the subjects in our series reported interest in receiving therapies aimed at improved QoL or tumor regression, even when OS remained unchanged. In the previously published literature, attitudes vary. While some reject drugs having a marginal benefit, others accepted therapies to alleviate symptoms or improve QoL, without prolonging OS.[48-51]

The comprehensive analysis cannot overlook the psychological and other endpoint consequences of prognostic awareness. In our series, subjects unaware of their prognosis had 10 percentage points better QoL compared to those who were well aware of their status; this improvement covered all QoL domains. Furthermore, accurate prognostic awareness involved more psychological symptoms, including anxiety, depression, concern about their health, and other adverse outcomes, in line with earlier studies.[8,16,17,52] In this regard, our data are similar to those of Nipp et al[8] who reported worse

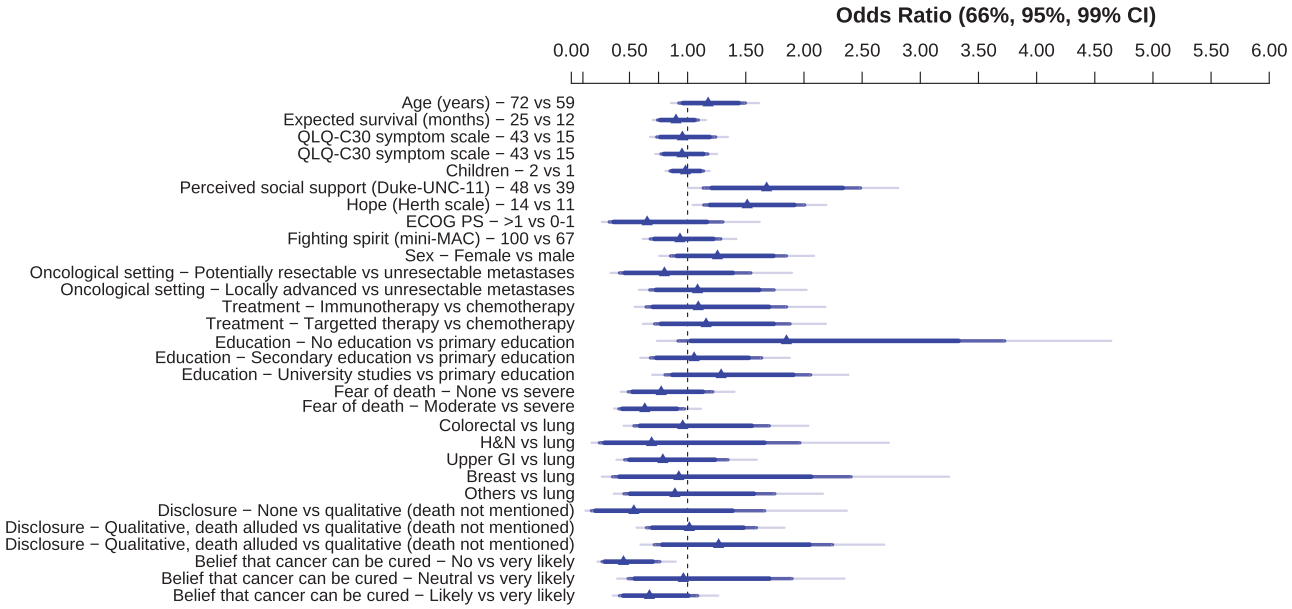

Figure 3. Proportional odds model to predict interest in low-efficacy therapies. The graph displays the odds ratios resulting from this model. The complete model is shown in Table 2. Interquartile effects are presented in the case of continuous variables. Odds ratios >1 denote greater belief that cancer can be cured. Abbreviations: ECOG PS, Eastern Cooperative Group performance status; H&N, head & neck cancer; FACIT, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale; QLQ-C30, European Organization for Research, and Treatment of Cancer Quality of Life C30 Questionnaire; mini-MAC, Mini-Mental Adjustment to Cancer Scale..

QoL and mood associated with accurate prognostic awareness, possibly interacting with certain coping profiles.

Thus, our study maps out 2 opposite poles, the ethical and the psychological one, of a moral dilemma that is posed at first appointments, during which the oncologists are apparently doomed to make a mistake, whatever decision they make.[53] On the one hand, they must carefully inform their patient, given that unrealistic expectations can entail agreeing to first-line treatments of scant usefulness or benefit, whose palliation-toxicity index may not be in line with individual preferences, in a context of ever-growing costs.[1] On the other hand, reluctance to fully disclosure the patient's prognosis seeks to circumvent the psychological impact, under the premise that not all patients have the same needs or preferences; that they sometimes simultaneously "want and don't want" to hear their death sentence, and oftentimes caregivers do not agree with information that is too negative. A possible solution to this dilemma is to adopt a patient-centered approach to communication taking into account factors such as health literacy level, cultural background, and emotional state.[54-56] For example, some patients may prefer direct and fact-based communication while others may benefit from a more empathetic and supportive approach. The timing of discussions about prognosis and treatment options is also important. While it is crucial to fully inform patients from the beginning, overwhelming them with too much information during their initial visit may be counterproductive. Oncologists may need to consider breaking down information into smaller, more manageable pieces and providing ongoing support and education throughout the patient journey. Ultimately, by working together with patients to develop a shared understanding of different treatment options' potential benefits and limitations, oncologists can empower them to make informed decisions that align with their values and care goals.

Our study should be interpreted in the context of its limitations. The first is the cultural dependence on the belief in curability. Nevertheless, our outcomes are comparable to those observed in other populations.[11] Second, the data refer solely to the first appointment with the oncologist and no longitudinal measurements have been made. Yet, the information extracted from the first visits is relevant, inasmuch as this is when treatment foundations are established, capturing the ethical dilemma of these appointments. Third, the questionnaire administered may not have epitomized such a subtle construct as belief in curability with the necessary specificity (ie, some patients report the desire to be cured more than the belief itself). It is also possible that fear focuses patients' attention on the short term or leaves them to forget the details of the appointments.[57] Therefore, caution must be exercised when interpreting self-reported questionnaires until a validated, multidimensional tool is available.[58,59] Since the study was cross-sectional, it is challenging to establish a clear cause-and-effect relationship between variables. Therefore, the reported impact of prognostic awareness on several endpoints is better understood as a correlation. Further investigation is required to understand the complex interplay between these factors. Finally, we based the definition of "low-efficacy therapy" on a fixed value (6 months), which may be clinically relevant in tumors with poor prognosis.

When interpreting the results of this study, it is crucial to bear in mind that the focus was on exploring the ethical implications of treatment decision-making at the time of initial cancer diagnosis with an oncologist. The hypothesis was that lack of knowledge about prognosis could impact treatment decisions. The study's findings highlight the interplay between multiple factors, such as fear of death, information received, and symptoms, which collectively influence belief in curability and interest in low-efficacy therapies. These findings underscore the importance of improving communication between clinicians and patients to ensure fully informed and

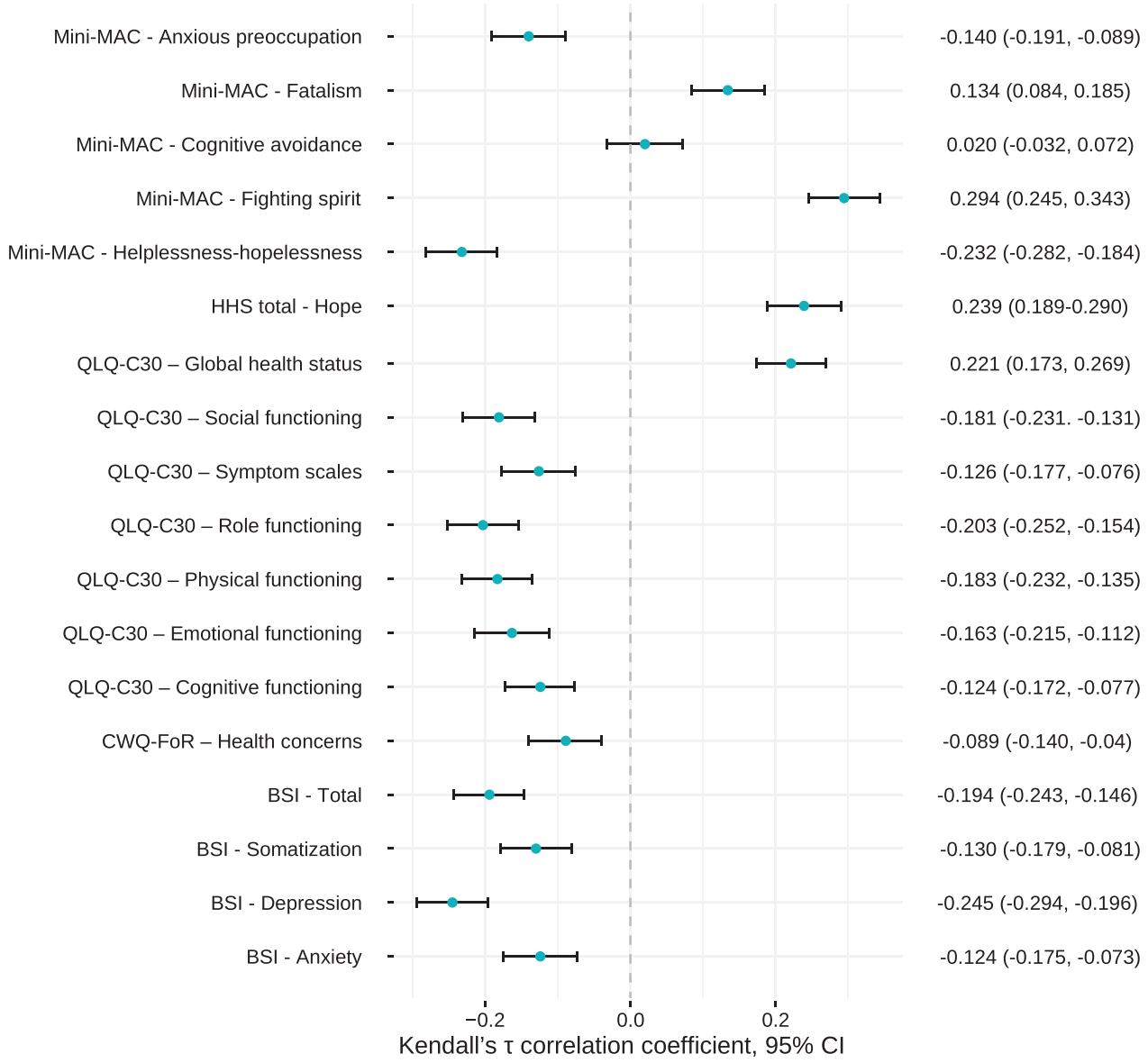

Figure 4. Kendall's τ correlation coefficients between the belief in curability and different scores. Abbreviations: BSI, Brief Symptom Inventory-18; CWQ-FoR, Cancer worry (for health) questionnaire; HHS, Herth Hope Scale; Mini-MAC, Mini-Mental Adjustment to Cancer Scale; QLQ-C30, EORTC Core Quality of Life questionnaire; see questionnaires in Supplementary material. Interpretation of higher scores: QLQ-C30 global scale, higher level of QoL; for other QLQ-C30 scales, greater symptom burden or function impairment.

ethical treatment decision-making. Furthermore, it is noteworthy that patients' awareness of prognosis may increase over time during cancer treatment, which could affect their interest in certain therapies, such as after learning about tumor progression.

Taking into account these limitations, our study suggests that misunderstandings regarding prognosis remain common, have repercussions on the patient's mood, and condition-informed decision-making. Ethical and psychological considerations guide decision-making in a trade-off in which for some to gain autonomy, while others lose in QoL and mood. Each person's specific circumstances must be understood to gauge the consequences of gain or loss of information on a case-by-case basis.

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Ethics Statement

NEOetic study was approved by the Research Ethics Committee of the Principality of Asturias (May 17, 2019) and by the AEMPS (May 8, 2019). The studies have been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study is an observational, non-interventionist trial. Signed informed

consent was obtained from all patients. Informed consent and approval by the national competent authorities including permission for publication and diffusion of the data were obtained.

Conflict of Interest

Alberto Carmona-Bayonas reported travel grants from Ipsen Spain. The other authors indicated no financial relationships.

Author Contributions

Conception/design: A.C.-B., A.R.-G., T.G.-G., C.C., P.J.-F. Provision of study material or patients: All authors. Collection and/or assembly of data: All authors. Data analysis and interpretation: A.C.-B., A.R.-G., T.G.-G., C.C., P.J.-F. Manuscript writing: A.C.-B., A.R.-G., T.G.-G., C.C., P.J.-F. Final approval of manuscript: All authors.

Data Availability

Statistical analyses were performed using R v4.05 statistical software, including the rms library. Patients are identified by an encrypted code only known by the local researcher. The code is available in the Supplementary material. The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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RESEARCH ARTICLE

Impact of systemic cancer treatment on quality of life and mental well-being: a comparative analysis of patients with localized and advanced cancer

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Abstract

Introduction This study investigated the impact of systemic cancer therapy on the quality of life, mental well-being, and life satisfaction of cancer patients.

Methods This prospective study was promoted by the Spanish Society of Medical Oncology (SEOM) and enrolled patients with localized, resected, or unresectable advanced cancer from 15 Spanish medical oncology departments. Patients completed surveys on quality of life (EORTC-QoL-QLQ-C30), psychological distress (BSI-18) and life satisfaction (SWLS) before and after systemic cancer treatment.

Results The study involved 1807 patients, 944 (52%) having resected, localized cancer, and 863 with unresectable advanced cancer. The mean age was 60 years, and 53% were female. The most common types of localized cancer were colorectal (43%) and breast (38%), while bronchopulmonary (32%), non-colorectal digestive (23%), and colorectal (15%) were the most frequent among those with advanced cancer. Before systemic treatment, patients with advanced cancer had poorer scores than those with localized cancer on physical, role, emotional, cognitive, social limitations, symptoms, psychological distress, and life satisfaction (all $p < 0.001$), but there were no differences in financial hardship. Patients with localized cancer had greater life satisfaction and better mental well-being than those with advanced cancer before systemic treatment ($p < 0.001$). After treatment, patients with localized cancer experienced worsening of all scales, symptoms, and mental well-being ($p < 0.001$), while patients with advanced disease had a minor decline in quality of life. The impact on quality of life was greater on all dimensions except economic hardship and was independent of age, cancer location, and performance status in participants with resected disease after adjuvant chemotherapy.

Conclusion In conclusion, our study highlights that systemic cancer treatment can improve quality of life in patients with advanced cancer, while adjuvant treatments for localized disease may have a negative impact on quality of life and psychological well-being. Therefore, treatment decisions should be carefully evaluated on an individual basis.

Keywords Cancer · Psychological distress · Quality of life · Satisfaction with life · Treatment

Introduction

Cancer is increasingly prevalent in our society, posing a health challenge that impacts patients physically, emotionally, socially, and economically [1]. Recent advances in detection and treatment have increased survival rates, resulting in a predicted 30% increase in prevalence over the next decade. Furthermore, population aging has contributed to the rising incidence; at 2021, there were 19.3 million cases worldwide, with this number expected to reach 28.9 million by 2040 [2, 3].

Quality of life in cancer patients is recognized as a dynamic, multi-dimensional concept that encompasses all aspects of the patient's life and needs, evaluating the balance between the current and ideal circumstances at any given moment [4, 5]. Studies indicate that cancer patients experience a decline in quality of life when compared to

Extended author information available on the last page of the article

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the general population [6, 7]. This decrease is attributed to the disease process, the treatment, and its duration, which in patients with unresectable advanced illness is typically sustained for life. Various somatic, emotional, and socioeconomic issues that patients develop at different stages of the disease further contribute to this decline in quality of life.

Various studies have indicated that somatic symptoms experienced by patients can lead to a greater degree of disability and lower quality of life, with a higher prevalence in patients with more advanced diseases and those undergoing longer treatments [8–10]. These studies have demonstrated how oncological patients can experience a deterioration in their functional state, resulting in limitations to daily physical activity and the presence of somatic symptoms [8]. Pain is present in up to 72% of patients [11], and other symptoms, such as dyspnea, weight loss, loss of appetite, constipation, nausea, and vomiting, in up to 60% of cases [12]. Sleep disturbances occur in up to 38%, and severe fatigue appears in 90% of cases, particularly in advanced stages of cancer [8, 13–15].

A recent study involving 768 cancer patients revealed a high frequency of social discomfort, with 98.3% of those surveyed feeling uneasy in social situations [11]. This statistic, coupled with findings from other studies that 54% of oncology patients treated with chemotherapy experience depression [11], as well as high rates of adjustment disorders, anxiety, life dissatisfaction, fear and uncertainty about the disease and its prognosis [16, 17], suggests that cancer has a significant psychological and social impact on those affected.

Improving a patient's quality of life in the context of cancer can lead to better outcomes. While the exact connection between quality of life and survival in those with localized cancer is not yet clear, studies have found a relationship between the two in patients with advanced cancer [18, 19]. Oncology teams are aware of the importance of quality of life and strive to improve it by mitigating the physical and psychological symptoms caused by the disease and its treatments [20]. In some cases, particularly with advanced tumors, enhancing quality of life is the primary objective of treatment. Moreover, quality of life is essential to a patient's recovery and should be at the forefront of all cancer care plans.

With these premises in mind, this study assesses the Influence of systemic therapy on the quality of life, mental well-being, and satisfaction with life of cancer patients, aiming to identify any populations that may have particularly severe deterioration in quality of life as a result of treatment.

Material and methods

Study design and population

This prospective study, promoted by the Bioethics Section of the Spanish Society of Medical Oncology (SEOM), involved fifteen medical oncology departments. Patients were enrolled consecutively in two cohorts; one group consisted of those with localized, resected cancer, while the other one had advanced, unresectable disease.

Before signing the informed consent form, all adult patients with a histologically confirmed diagnosis of malignancy were invited to participate in the study at their initial visit with the medical oncologist. Eligible participants included adults aged 18 years and older with a non-advanced cancer resected with curative intent eligible for adjuvant therapy, as well as those with an unresectable advanced cancer who were candidates for systemic cancer treatment at the oncologist's discretion. Exclusion criteria included a contraindication to antineoplastic treatment, systemic therapy in the last two years for this or another advanced cancer, or an underlying mental and/or medical condition that could hinder the person's ability to participate in the study. Questionnaires were filled out by the subject at home after the visit with the oncologist, prior to administration of systemic cancer treatment and again after completion of adjuvant cancer treatment, approximately 6 months later (localized cancer) or after the first imaging study to assess response to treatment 2–3 months later (advanced cancer). We screened 1,893 patients between 2019 and 2022, of whom 1,807 were eligible for analysis and 96 were excluded for not meeting the inclusion criteria ($n = 30$), meeting exclusion criteria ($n = 45$), or having incomplete data ($n = 21$).

Clinical data were collected and updated by the oncologist via two web platforms, www.neocoping.es (localized cancer) and www.neoetic.es (advanced cancer). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [21] and with the ethical standards. It was approved by the Medical Research Ethics Committees of each participating hospital and the Spanish Agency for Medicines and Health Products (AEMPS) (identification code ES: 14042015). Data collection procedures were consistent across all hospitals and data related to participants were obtained from the institutions where they received treatment. Participation in the study was completely voluntary, anonymous, and in no way affected patient care.

Variables

The information was collected and updated by medical oncologists especially trained to meet the study's requirements. Demographic and clinical data (age, biological sex, performance status, comorbidities, marital status, educational level, employment status, tumor location and stage, and systemic cancer treatment) were obtained directly from patients and records. Prior to initiation of treatment, patients underwent a baseline assessment via the administration of three standardized questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QoL-QLQ-C30), the Satisfaction with Life Scale (SWLS) and the Brief Symptom Inventory 18 (BSI-18). Upon completion of adjuvant therapy, participants with localized disease underwent reevaluation with the EORTC-QoL-QLQ-C30 and BSI-18 questionnaires, while subjects with advanced disease underwent a similar assessment following the initial imaging study to evaluate disease progression. Satisfaction with Life Scale (SWLS) scores were obtained only at baseline to ascertain how participants rated their life after cancer diagnosis. The details of these questionnaires are provided below [22–24].

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QoL-QLQ-C30) is a 30-item scale consisting of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer sufferers (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and perceived financial impact of the disease [25]. Each item is scored on a 0–100 scale, with higher scores representing a higher level of functioning for the functional scales and a higher symptom burden for the symptom scales. The Cronbach's alpha for Spanish cancer patients was 0.86 [24].

The Satisfaction with Life Scale (SWLS) is a 5-item scale designed to measure an individual's overall life satisfaction [26]. Respondents were asked to indicate their level of agreement with each statement on a seven-point Likert-type scale, and raw scores ranged from 5 to 35, with higher scores indicating higher life satisfaction. The internal consistency of the scale for Spanish cancer patients was $\alpha = 0.91$ [27].

The Brief Symptom Inventory (BSI-18) is a self-reported questionnaire consisting of 18 items that evaluate a respondent's mental well-being over the past week [28]. The scale includes symptoms of depression (dysphoric mood, anhedonia, and self-deprecation) anxiety (nervousness, tension, and apprehension), and somatization (distress caused by the perception of bodily dysfunction). Each item is rated on a 5-point Likert scale, with 0 representing 'not at all' and 4 representing 'extremely'. Raw score is converted to T-scores, based on sex-specific normative data. The Spanish version of the BSI-18 has demonstrated good reliability; Cronbach's alpha was 0.88 [29].

Statistical analyses

This study utilized descriptive statistics to analyze demographic data and survey responses. Categorical data was evaluated using absolute frequencies and quantitative data was assessed using means and standard deviations. Furthermore, patients were grouped according to type of cancer to perform further descriptive analyses. We used bivariate chi-square and *t* tests to assess differences between subjects with localized and advanced cancer in terms of sociodemographic, clinical, and psychological characteristics. Additionally, analysis of variances was used to probe differences in psychological characteristics (as measured by the quality of life, psychological distress, and satisfaction with life scales) according to group status (advanced or resected cancer). Eta Squared (η^2) was applied to quantify the magnitude of effect of continuous variables. According to the literature, η^2 values of approximately 0.01, 0.06, and greater than 0.14 indicate small, medium, and large effect sizes, respectively. Similarly, a Multivariate Analysis of Covariance was performed to investigate the influence of pretest levels and group status (advanced and resected cancer) on psychological characteristics (quality of life, psychological distress, and satisfaction with life scales), adjusted for age, tumor site, and performance status. The analysis was conducted with IBM SPSS Statistics for Windows, version 23.0.

Results

Baseline characteristics

Of the 1,807 eligible patients, 52% had a localized, resected cancer, and 48% had unresectable advanced cancer. Baseline sociodemographic and clinical characteristics of the patients are presented in Table 1. The median age of participants with localized and advanced disease was 59.0 and 65 years, respectively. Men presented more frequently than women with advanced cancer. The proportion of subjects who were not working was higher in the advanced disease group (mostly retired), while in localized disease cohort, most of those who were not working were unemployed or on sick leave. The most common tumors were colorectal (43%) and breast (38%) among the localized cancer group, and bronchopulmonary (32%), non-colorectal digestive (23%), and colorectal (15%) in participants with advanced cancer. Patients with localized disease underwent surgery and received adjuvant chemotherapy; 67% received

Table 1 Demographic and clinical characteristics of patients

Demographic and clinical characteristics	Total ($n=1807$)	Localized cancer ($n=944$)	Advanced cancer ($n=863$)	$t/\chi 2$	p
Sex: *n* (%)					
Men	843 (47)	370 (39)	473 (55)	44.163	0.001
Women	964 (53)	574 (61)	390 (45)		
Age (years): mean (SD)	60 (11)	59 (12)	65 (11)	− 11.825	0.001
Marital Status:					
Married/partnered: *n* (%)	1301 (72)	719 (76)	582 (67)	17.028	0.001
Educational level: *n* (%)					
Basic	919 (51)	509 (54)	410 (48)	7.414	0.006
Intermediate	888 (49)	435 (46)	453 (52)		
Unemployed: *n* (%)	849 (47)	393 (42)	456 (53)	22.735	0.001
Cancer: *n* (%)					
Bronchopulmonary	320 (18)	43 (5)	277 (32)	543.32	0.001
Colorectal	534 (30)	403 (43)	131 (15)		
Non-colorectal digestive	268 (15)	69 (7)	199 (23)		
Breast	458 (25)	357 (38)	101 (12)		
Type of systemic treatment					
Chemotherapy (CT)	1124 (60)	669 (67)	455 (53)	777.53	0.001
CT and radiotherapy	335 (18)	335 (33)	0 (0)		
Immunotherapy with/without CT	62 (3)	0 (0)	62 (7)		
Targeted therapy with/without CT	46 (3)	0 (0)	46 (5)		
Others	300 (16)	0 (0)	300 (35)		
Death *n* (%)	93 (5%)	22 (2)	71 (8)	36.205	0.001

n = number, *SD* standard deviation

chemotherapy alone, and 33% received chemotherapy combined with radiotherapy. Patients with advanced disease were treated with chemotherapy alone (53%), immunotherapy with or without chemotherapy (7%), or targeted therapy with or without chemotherapy (7%).

Comparison of quality of life, mental well-being, and life satisfaction among patients with localized or advanced cancer before starting systemic treatment

The results of the quality of life questionnaire revealed that the sample with advanced cancer had poorer scores on physical, role, emotional, cognitive, and social limitations (all $p<0.001$) (Table 2). In addition, these patients reported more symptoms on all symptom scales (fatigue, nausea, pain, dyspnea, insomnia, loss of appetite, and diarrhea) (all $p<0.001$). There were no differences in the financial hardship scale between the two cohorts. At baseline, participants with advanced cancer had more functional limitations, more symptoms, and worse health status (all $p<0.001$) compared to those with localized cancer. Notably, subjects with localized cancer enjoyed greater life satisfaction and better mental well-being than those with advanced cancer prior to the start of systemic treatment ($p<0.001$).

Psychological and somatic changes after cancer treatment

Among participants in the group with localized resected cancer, 624 completed follow-up questionnaires after finishing their adjuvant cancer treatment. Our dropout rate was 34%, relatively small for this type of study. In our case, 66% ($n=210$) was due to patient reasons (i.e., reasons known only to the patient), 27% ($n=88$) for medical reasons (i.e., toxicity, disease progression), and 7% ($n=22$) attributable to death. In the sample with advanced cancer, 330 completed the follow-up questionnaires after the first imaging study to assess response to treatment and 71 died, while 462 were lost to follow-up as a result of premature withdrawal of treatment owing to progression or clinical decline.

After comparing baseline and post-treatment scores on quality of life and psychological distress scales and adjusting for age, primary tumor site, and Eastern Cooperative Oncology Group (ECOG) performance status, a greater deterioration in quality of life was observed among individuals with localized disease, with a significant increase in all symptoms

Table 2 How Cancer Extent Affects Quality of Life, Psychological Well-Being, and Life Satisfaction

	Total ($n=1807$)	Localized cancer ($n=944$)	Advanced cancer ($n=863$)	F	p	Eta squared
Quality of Life (EORTC QoL-QLQ-C30)[a]: Mean (SD)						
Physical function	79.1 (22.9)	85.9 (15.6)	71.6 (26.9)	**193.689**	**0.001**	**0.097**
Role function	72.5 (30.6)	76.3 (26.3)	68.4 (34.2)	**30.449**	**0.001**	**0.017**
Emotional function	67.9 (27.4)	72.1 (24.9)	63.4 (29.4)	**45.271**	**0.001**	**0.025**
Cognitive function	81.9 (23.7)	85.6 (20.7)	78.0 (26.0)	**47.512**	**0.001**	**0.026**
Social function	72.6 (30.2)	77.1 (25.4)	67.8 (34.1)	**43.011**	**0.001**	**0.023**
Fatigue	36.9 (29.1)	29.1 (24.3)	45.4 (31.5)	**150.468**	**0.001**	**0.077**
Nausea/emesis	12.6 (23.9)	8.9 (18.3)	16.5 (28.2)	**46.508**	**0.001**	**0.025**
Pain	26.2 (30.3)	17.9 (23.2)	35.2 (34.2)	**158.575**	**0.001**	**0.081**
Dyspnea	8.9 (22.6)	4.9 (15.8)	13.3 (27.5)	**63.922**	**0.001**	**0.034**
Insomnia	37.4 (35.6)	31.2 (32.2)	44.2 (37.9)	**61.818**	**0.001**	**0.033**
Appetite loss	26.8 (34.9)	20.1 (29.5)	34.1 (38.7)	**76.059**	**0.001**	**0.041**
Constipation	27.8 (35.5)	20.9 (30.1)	35.2 (39.2)	**75.757**	**0.001**	**0.041**
Diarrhea	16.7 (29.2)	13.6 (24.3)	20.2 (33.3)	**23.365**	**0.001**	**0.013**
Financial difficulties	16.7 (30.1)	15.6 (28.6)	18.0 (31.7)	2.647	0.104	0.001
FUNCTIONAL scale	74.7 (20.7)	79.3 (17.1)	69.8 (23.1)	97.417	**0.001**	**0.052**
SYMPTOM scale	23.4 (18.4)	18.1 (14.9)	29.2 (20.1)	174.748	**0.001**	**0.089**
HEALTH status Scale	65.3 (23.1)	70.2 (20.2)	60.1 (24.8)	90.517	**0.001**	**0.048**
Satisfaction with life (SWLS)[b]	26.4 (6.3)	27.0 (5.8)	25.7 (6.7)	19.096	**0.001**	**0.011**
Psychological distress (BSI)	65.3 (7.4)	63.7 (7.1)	67.1 (7.4)	97.968	**0.001**	**0.052**

Bold values indicate significance at the 5% level

EORTC-QoL-QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *SWLS* Satisfaction with life scale

[a]Scale from 0 to 100

[b]Scale from 5 to 35 for satisfaction with life

(Table 3). In comparison, patients with advanced disease experienced a minor worsening of quality of life. The impact on quality of life was greater on all dimensions except economic hardship and was independent of age, cancer location, and performance status in participants with resected disease after completion of adjuvant chemotherapy.

Discussion

In this research, it was witnessed that patients with advanced neoplasia have lower quality of life, greater psychological suffering, and reduced satisfaction with life before the onset of systemic cancer treatment compared to those with resected (cured) localized cancer. Upon follow-up appraisal, the latter group experienced a larger decline in quality of life than those with advanced cancer.

Historically, systemic cancer treatments focused on increasing patient survival. However, this perspective has shifted, and various tools are now employed to measure the quality of life of patients during cancer treatment, allowing for a risk–benefit ratio assessment that evaluates not only median survival but also the quality of life during the treatment period [29, 30]. Particularly, it is desirable to find treatments that improve both survival and quality of life in patients with advanced disease, as treatments for this group often provide limited survival benefits [31, 32]. To date, no studies have compared the impact of systemic cancer treatments on quality of life for patients who have been cured (localized) and those with incurable cancer (advanced).

Consistent with global cancer statistics [34], our sample displayed an increased frequency of advanced cancer in elderly males, primarily located in the pulmonary and gastrointestinal systems, for whom systemic treatment mainly involve chemotherapy, and to a lesser extent, targeted therapies, or immunotherapy. Conversely, for patients with early-stage cancer, our sample showed a larger proportion of females, predominantly young, with the most common malignancies being breast and colon cancer, and treatment consisting of adjuvant chemotherapy, either alone or in conjunction with radiotherapy [20]. This disparity is attributable to the high incidence of breast and colon cancer in localized stages, neoplasms for which screening programs enable early diagnosis and treatment in the form of surgery and adjuvant

Table 3 Analysis of variance of repeated measurements before and after systemic treatment adjusted for age, tumor site, and ECOG performance status ($n=954$)

Scales	Localized cancer ($n=624$)		Advanced cancer ($n=330$)		MANCOVA results, F		
	Pre mean (SD)	Post mean (SD)	Pre mean (SD)	Post mean (SD)	Time* tumor	Time	Tumor condition
Psychological distress (BSI)	66.9 (7.4)	67.0 (7.4)	64.5 (7.1)	65.5 (6.9)	**19.161**	0.415	**22.595**
Quality of life (EORTC-QLQ-C30)							
Physical fun	86.2 (15.1)	72.3 (26.3)	83.6 (17.9)	74.9 (24.2)	2.913	0.001	**63.297**
Role fun	76.5 (25.9)	70.4 (33.1)	75.8 (27.4)	73.2 (30.9)	0.343	1.329	**6.558**
Emotional fun	72.3 (24.6)	65.4 (29.8)	76.0 (25.2)	72.5 (27.2)	**3.939**	**6.533**	**10.201**
Cognitive fun	85.9 (20.3)	79.8 (23.9)	82.7 (23.1)	79.7 (24.4)	0.959	0.416	**8.895**
Social fun	77.7 (25.1)	69.2 (32.2)	76.7 (27.0)	72.1 (31.4)	1.341	1.325	**21.666**
Fatigue	28.3 (23.8)	44.6 (31.0)	35.7 (27.5)	38.9 (30.2)	**16.909**	0.767	**31.008**
Nausea/emesis	8.8 (17.0)	17.0 (28.9)	10.9 (20.1)	13.8 (24.8)	**8.681**	2.648	**11.428**
Pain	17.1 (23.1)	34.8 (34.0)	20.0 (26.3)	24.5 (29.4)	**21.285**	3.011	**45.526**
Dyspnea	4.5 (14.9)	11.8 (25.2)	6.6 (19.0)	10.2 (23.1)	1.807	0.846	**19.828**
Insomnia	30.7 (31.9)	42.0 (38.1)	32.1 (33.3)	31.9 (35.4)	**14.433**	**9.704**	**6.437**
Appetite loss	16.5 (29.2)	34.1 (39.6)	20.4 (30.2)	27.3 (33.6)	2.819	0.070	**11.408**
Constipation	20.8 (29.9)	35.0 (38.9)	22.9 (31.3)	29.1 (34.3)	**6.374**	0.965	**22.569**
Diarrhea	12.7 (22.5)	19.6 (33.3)	15.7 (26.5)	22.4 (32.9)	0.275	0.974	**15.395**
Financial	15.2 (27.7)	17.2 (31.6)	13.7 (27.4)	15.7 (29.8)	0.669	**7.175**	2.545
FUNCTIONAL s	79.7 (16.8)	71.4 (21.9)	79.0 (19.5)	74.5 (22.1)	2.625	1.451	**27.281**
SYMPTOM s	17.5 (14.1)	28.5 (20.2)	19.8 (17.2)	23.8 (18.4)	**18.229**	**6.238**	**42.266**
HEALTH s	71.1 (19.7)	60.7 (25.3)	68.7 (23.6)	59.3 (26.6)	0.052	0.432	**38.249**

EORTC-QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *Pre* before adjuvant treatment, *Post* after adjuvant treatment, *fun* function, *s* scale, *SD* Standard Deviation

Adjusted by age, tumor site and ECOG performance status

Bold values indicate significance at the 5% level

therapy [34, 35]. Bearing these anticipated differences in mind and aiming to appraising the behavior of people with localized or advanced cancer receiving similar treatment, yet with clearly distinct population characteristics, the research conducted has been adjusted for age, primary tumor site, and performance status.

We observed poorer quality of life in our series of participants with advanced cancer prior to initiating systemic treatment compared to those with localized cancer, mainly due to the presence of more physical symptoms, such as fatigue and pain, which aligns with other studies [8, 11] Similarly, a higher prevalence of dyspnea, insomnia, weight loss, constipation, and diarrhea were observed. Understandably, patients with advanced, unresectable cancers have both primary malignancy and metastases, affecting multiple organs and organ functions, whereas the localized cancer cohort does not, as their cancers have been surgically removed. Among this population, insomnia, fatigue, and loss of appetite were the most severe symptoms, which may be the result of early post-surgical complications [36].

Conversely, we observed that prior to commencing treatment, subjects with advanced illness present with greater emotional, cognitive, and social impairment, which may be attributable to less successful coping with their often incurable cancer, necessitating a more involved psychological process [37]. Additionally, a decline in quality of life as a consequence of a higher prevalence of somatic symptoms hinders their ability to pursue regular social activities [11]. Furthermore, we discovered that individuals with unresectable advanced cancer have lower baseline life satisfaction. No differences in economic hardship were revealed among the patients, which can be ascribed to the free public healthcare system in Spain, granting universal access to assessments and therapeutic services, where-upon during cancer therapy, citizens are entitled to sick pay.

Following adjuvant treatment (localized cancer cohort) and the initial response assessment imaging study (advanced cancer cohort), all analyzed scales exhibited a decline, as well as increased symptoms in the group with localized disease. It is crucial to consider that the treatment goal for these individuals is to achieve a cure and minimize the risk of recurrence. Given the more favorable results for the advanced disease cohort, the administration of toxic treatments with a temporary impact on QoL is deemed acceptable [38]. Nevertheless, it is important to emphasize that, according to multiple studies, some adverse effects of

adjuvant treatment may have long-term consequences [39, 40]. In advanced disease, the rating scores exhibited only minimal changes. Some studies demonstrate different cut-off levels for clinical relevance, higher than those in this work [41–44]. Thus, the changes detected here appear not to be clinically relevant. This is likely because the cancer treatments decrease tumor load and symptoms, while preserving quality of life. Interestingly, improved quality of life post-chemotherapy has also been observed [45] . Careful assessment of the risk–benefit of treatments likely to avoid serious toxicities has contributed to preserving this group's quality of life.

The completion of adjuvant treatment often leads to a decline in the health of patients with localized cancer, which must be considered when observing them post-treatment, as they may have long-term effects that can impede social and occupational reintegration. In contrast, those with advanced cancer frequently maintain their quality of life when monitored, likely due to successful tumor control with treatment and a beneficial balance of benefits and risks determined by the oncologist.

This study has certain limitations. First, two groups of patients with different baseline characteristics were compared, and calculations were adjusted for age, primary tumor site, and performance status to reduce potential confounding factors. Second, this study was conducted in a Spanish oncology population, and caution is required when generalizing the results to other countries, particularly those outside of the Western world, as cancer care can vary widely depending on health system organization and the country's economy, with Spain having universal access to public healthcare. Third, since the study sample consisted solely of Caucasian participants, the findings may not be generalizable to other racial groups. Fourth, only 56% of the participants had completed the questionnaires at follow-up, with losses largely due to clinical decline or death in the advanced disease cohort or non-completion of adjuvant treatment in the localized disease group. This resulted in the exclusion of the most deteriorated subjects. Finally, the questionnaires were completed by the patient in their own home without supervision.

Conclusions

Our study reveals that systemic cancer treatment is a valuable strategy to enhance survival rates and maintain quality of life in people with advanced cancer. Moreover, we have observed that adjuvant treatments with curative intent, administered to individuals with localized disease, can adversely affect their quality of life and psychological well-being. This is not the case for patients with advanced cancer, in whom antineoplastic treatment preserves their quality of life and, therefore, improves their psychological well-being. Further research is necessary to identify specific subpopulations at risk for experiencing a pronounced decrease in quality of life. This information would enable early prevention programs aimed at lessening the physical and psychological repercussions of systemic cancer treatment to be developed and implemented.

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Author contributions ACB, CC and PJF contributed to the study conception, design, and analysis. Material preparation and data collection were performed by ARG, ACB, RH, PCC, VV, MAB, DLE, MJC, MGM, ACT, PJF, EE, and CC. The first draft of the manuscript was written by ARG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and material Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software, 25.0 version (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). The code is available upon request to the authors.

Code availability Patients are identified by an encrypted code known only to the local researcher. The code of the analyses is available upon request to the authors.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interest to disclose.

Ethics approval This study was approved by the Research Ethics Committee of the Principality of Asturias (May 17, 2019) and by the AEMPS (May 8, 2019; number: D57DG38BFB). The studies have been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study is an observational, non-interventionist trial.

Consent to participate Signed informed consent was obtained from all patients.

Consent for publish Informed consent and approval by the national competent authorities includes permission for publication and diffusion of the data was obtained.

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Health and Quality of Life Outcomes

RESEARCH

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Using the emotional functioning in clinical practice to detect psychological distress in patients with advanced thoracic and colorectal cancer

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Abstract

Purpose Patients with advanced cancer suffer significant decline of their psychological state. A rapid and reliable evaluation of this state is essential to detect and treat it and improve quality of life. The aim was to probe the usefulness of the emotional function (EF) subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EF-EORTC-QLQ-C30) to assess psychological distress in cancer patients.

Methods This is a multicenter, prospective, observational study involving 15 Spanish hospitals. Patients diagnosed with unresectable advanced thoracic or colorectal cancer were included. Participants completed the Brief Symptom Inventory 18 (BSI-18), the current the gold standard, and the EF-EORTC-QLQ-C30 to assess their psychological distress prior to initiating systemic antineoplastic treatment. Accuracy, sensitivity, positive predictive value (PPV), specificity, and negative predictive value (NPV) were calculated.

Results The sample comprised 639 patients: 283 with advanced thoracic cancer and 356 with advanced colorectal cancer. According to the BSI scale, 74% and 66% displayed psychological distress with an EF-EORTC-QLQ-C30 accuracy of 79% and 76% in detecting psychological distress in individuals with advanced thoracic and colorectal cancer, respectively. Sensitivity was 79 and 75% and specificity was 79 and 77% with a PPV of 92 and 86% and a NPV of 56 and 61% (scale cut-off point, 75) for patients with advanced thoracic and colorectal cancer, respectively. The mean AUC for thoracic cancer was 0.84 and, for colorectal cancer, it was 0.85.

Conclusion This study reveals that the EF-EORTC-QLQ-C30 subscale is a simple and effective tool for detecting psychological distress in people with advanced cancer.

Keywords Advanced cancer, Emotional function, EORTC-QLQ-C30, Psychological distress, Sensitivity, Specificity

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Introduction

In recent years, improvements in cancer treatments and early detection have led to better prognosis and survival for subjects with thoracic and colorectal cancer [1–4]. However, a significant number of them still develop advanced, untreatable cancers and undergo treatments to extend survival, but often at the expense of diminished quality of life due to treatment toxicity and dosing [5–7]. This decline in quality of life is especially pronounced in advanced and end-of-life patients [6–8].

Cancer patients suffer a high incidence of psychological distress, with rates ranging from 42 to 90% depending on the type of cancer, stage, and population studied [9–11]. According to Carrozzino [12], psychological distress can be defined as a subjective, multi-dimensional, transdiagnostic construct that encompasses feelings of discomfort, demoralization, mental pain, anguish, somatic symptoms, and self-criticism. These individuals also exhibit a high prevalence of depression, anxiety, and adjustment disorders [13–15]. This is especially true in patients with thoracic and colorectal cancer, which are two of the leading types of cancer in terms of incidence and mortality [6, 8, 16]. Emotional distress has shown strong associations with decreased physical activity and symptoms such as pain and fatigue in patients with lung [17, 18], gastric [6], and colorectal cancer [19]. Psychological state assessment is common in clinical trials [20] as one of the domains included in quality of life questionnaires [21].

This psychological distress can affect treatment, worsening its tolerability, potentially impacting outcomes, increasing the risk of suicide, and early patient demise [22]. Such is the negative impact of these psychological symptoms on activities of daily living and health-related quality of life (HRQoL) in cancer patients that the American Society of Clinical Oncology (ASCO) recommends implementing quick screening instruments that assess psychological distress in cancer patients [23] and measures to mitigate its impact.

For the oncologist, the importance of having instruments available to rapidly appraise the person's psychological state lies in the fact that they typically have limited time to care for the patient during clinical visits and have to assess many symptoms and complications associated with cancer and its treatment, oftentimes making it difficult to adopt a comprehensive and effective approach to the psychological sphere. On the other hand, because of their general physical and psychological state, individuals with advanced cancer have a more limited ability to concentrate and answer questionnaires than the general population. Therefore, the emotional function (EF) subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30) can serve as a rapid screening scale to assess psychological distress in subjects with advanced cancer [24], especially since the EORTC-QLQ-C30 is the most used scale to measure quality of life in clinical trials in Spain [24, 25] and in the rest of the world [26, 27].

When using the EF subscale of the EORTC-QLQ30 (EF-EORTC-QLQ30) to identify people with psychological distress, a cut-off point < 66.7 is often used, following the distribution of scores in the general population [21]. Nevertheless, some authors have found a lower mean score in cancer patients [28], suggesting a cut-off point of < 0.46 [29], while others recommend using a cut-off point < 0.75 [28] or even < 90 [30] to identify cancer patients with psychological distress. There is currently no consensus on the standard cut-off point in subjects with cancer and there are no studies that have established a cut-off point in the scenario of advanced cancer. This study sought to determine the specificity, the sensitivity, and cutoff of the Emotional functioning subscale of the EORTC QLQ-C30 to detect psychological distress in patients with advanced thoracic cancer and colorectal cancer. The study assesses the hypothesis that a two-item component of the emotional functioning scale can be useful as an initial screening measure to identify advanced cancer patients at risk for psychological distress.

Methods

Study design and patients

NEOetic is an observational, prospective, multi-institutional study involving 15 medical oncology departments in Spain and promoted by the Bioethics Group of the Spanish Society of Medical Oncology (SEOM). The study protocol complied with the provisions of the Declaration of Helsinki, was approved by the ethics committees of each hospital and by the Spanish Agency of Medicines and Health Products (AEMPS; identification code: ES14042015). All eligible patients were identified by oncologists. Participants were informed that their participation was voluntary, anonymous, and confidential. Written informed consent was obtained from all participants prior to data collection. Participants were aged 18 years or older, had histologically confirmed, unresectable advanced thoracic or colorectal cancer, and were candidates for systemic therapy. Individuals with severe mental illness that could compromise study adherence were excluded. Thoracic cancer included all cancers occurring in the thoracic cavity, including cancers of the lung, pleura (mesothelioma), thymus, and trachea. Colorectal cancer included all cancers occurring in the large intestine from the ileocecal valve to the lower rectum. All cancers included were of epithelial origin; neoplasms of other types, such as neuroendocrine tumors, hematological tumors, and sarcomas were therefore excluded as

their management and prognosis are different from those of carcinomas.

Measures

The data collection procedures were similar in all hospitals. Clinical variables (type of tumor, pathological and molecular variables, cancer stage, treatment, performance status, and comorbidities) were obtained from the medical records and collected and updated by the medical oncologist who informed the patient of their diagnosis and prescribed antineoplastic therapy. These variables were compiled through a web platform (www.neoetic.es).

The subjects provided information concerning their age, sex, level of education, and occupational status, as well as the EORTC-QLQ-C30 an BSI-18 scales. The oncologist gave the questionnaires to each subject after shared treatment decision making. Questionnaires were filled out at home and handed in to the study assistants at the next appointment before starting systemic antineoplastic treatment.

The EF-EORTC-QLQ30 consists of four items that probe affective aspects of anxiety, depression, and general distress based on patients' perceptions of feeling tense, worried, depressed, and irritable [21]. Items are scored on a four-point Linkert scale from 0 ("not at all") to 4 ("very much") over a one-week period. Raw scores are transformed into a scale from 0 to 100 with higher scores indicating better functioning. For the purpose of this work, we established that a score ≤ 75 indicated a psychological problem and >75 meant "no problem" [31, 32]. In our sample, 49% had an EF score >75; Cronbach's α for the scale was 0.89. The Spanish version of the EF-EORTC-QLQ-C30 has demonstrated satisfactory reliability and validity in the Spanish population and a completion time of less than 3 min [24].

The BSI-18 is one of the most widely used instruments to assess psychological distress [33]. It is an 18-item scale containing three groups of six questions each that comprise the anxiety, depression, and somatization subscales [33]. It is scored on a 5-point Likert scale (0–4) based on a one-week recall period. The overall Global Severity Index (GSI) score ranges from 0–72 with higher scores evidencing greater anxiety or depression. Raw scores are converted to T-scores based on sex-specific normative data. In the present study, Cronbach's α values for the anxiety and depression scales were 0.87 and 0.74, respectively. The Spanish version of the BSI-18 has demonstrated its reliability and validity in Spanish patients [34].

Statistics

The BSI-18 questionnaire was used as the "gold standard" for comparison with the EF-EORTC-QLQ-C30. The BSI-18 applies the clinical case rule (39) originally developed for the SCL-90 to identify individuals with significant psychological distress (T-cut-off ≥ 63) [33]. According to our gold standard test, psychological distress designated by the EF-EORTC-QLQ-C30 was defined as true positive (TP, correctly identified as case), true negative (TN, correctly identified as non-case), false positive (FP, incorrectly identified as case), and false negative (FN, incorrectly identified as non-case). The following measures were calculated: (1) the number of correctly identified patients with psychological distress (overall test accuracy $[TP+TN]/[TP+TN+FP+FN]$); (2) the proportion of correctly identified positives (true positive/sensitivity rate, $TP/[TP+FN]$); (3) the proportion of correctly identified negatives (true negative/specificity rate, $TN/[TN+FP]$); (4) the proportions of TP (BSI-18) results (EF-ORTC-QLQ-C30) (positive predictive value, $TP/[TP+FP]$), and (5) the proportions of TN results (negative predictive value, $TN/[TN+FN]$). The discriminatory ability of the EF-EORTC-QLQ30 score was calculated using the area under the receiver operating characteristic (ROC) curve (AUC). The AUC summarized the ability of the EF-EORTC-QLQ-C30 to discriminate between patients with and without psychological distress. A higher AUC indicated better discriminatory capacity. We used a threshold AUC ≥ 0.70 for the EF-EORTC-QLQ-C30, which was also the standard used for our previous analysis [30, 35]. Analyses were performed with the IBM-SPSS 23.0 statistical software package for Windows PC.

Results

Patient baseline characteristics

A total of 660 consecutive patients agreed to participate in the study between February 2020 and December 2022. Twenty-one patients were excluded as they failed to meet the inclusion criteria. This resulted in a final sample of 639 participants of whom 283 had unresectable advanced thoracic cancer and 356 had unresectable advanced colorectal cancer.

Demographic and clinical characteristics are exhibited in **Table 1**. The advanced thoracic cancer cohort included cancer of the lung (82%, n = 232), esophagus (15%, n = 42), and pleura (3%, n = 9). The advanced colorectal cancer group included colon (80%, n = 284), rectal (18%, n = 64), and intestinal cancer (2%, n = 8). The subjects with a thoracic cancer were predominantly male (62%) with a mean age of 65.6 years (standard deviation (SD) = 9.5) and two thirds had stage IV cancer (78%). Those with colorectal cancer were also mainly male (61%) with a mean age of 66.0 years (SD = 10.6) and most had stage IV cancer (85%). No significant differences in psychological distress were revealed regarding age, gender, marital status, and education in individuals with thoracic or colorectal cancer.

Table 1 Patient baseline demographic characteristics

Demographic characteristics	Unresectable advanced thoracic cancer ($n=283$)	Unresectable advanced Colorectal Cancer ($n=356$)
Age (Mean ± Standard Deviation)	65.6 ± 9.5	66.0 ± 10.6
Gender (n, %)		
Male	176 (62)	218 (61)
Female	107 (38)	154 (39)
Marital status		
Married or partnered	219 (85)	281 (86)
Not partnered	64 (15)	75 (14)
Education		
≤ Primary	112 (39)	185 (52)
> High School	171 (61)	171 (48)
Employed		
Yes	147 (52)	199 (56%)
No (retired or unemployed)	136 (48)	157 (44%)
Clinical characteristics		
Stage (n, %)		
Locally advanced	63 (22)	54 (15)
IV	220 (78)	302 (85)
Histology		
Adenocarcinoma	146 (52)	300 (84)
Others	137 (48)	56 (16)
Estimated survival		
Less than 12 months	70 (25)	101 (28)
More than 12.1 months	213 (745)	255 (78)
First diagnosis of cancer		
No (recurrence)	37 (13)	59 (16)
Yes	246 (87)	297 (84)
Systemic treatment (n, %)		
Chemotherapy	197 (70)	337 (95)
Others without chemotherapy	86 (30)	19 (5)

Screening for psychological distress

In total, 210 patients (74%) with advanced thoracic cancer and 236 (66%) with colorectal cancer showed psychological distress according to the BSI-18 scale which, as previously mentioned, was deemed the gold standard. The mean BSI-18 score was 67.1 (SD = 7.5) in thoracic cancer and 66.1 (SD = 7.1) among participants with advanced colorectal cancer. The accuracy of the EF-EORTC-QLQ-C30 for detecting psychological distress was 79% among the thoracic cancer group and 76% in the colorectal cancer group using a cut-off point < 75. FPs were detected in 15 subjects with thoracic cancer and 27 with colorectal cancer. Considering these FPs, specificity was 79% in thoracic cancer and 77% in colorectal cancer. FNs were detected in 44 subjects with thoracic cancer and in 58 with colorectal cancer (Fig. 1). As a result of these FNs, sensitivity was 79% in thoracic cancer and 75% in colorectal cancer.

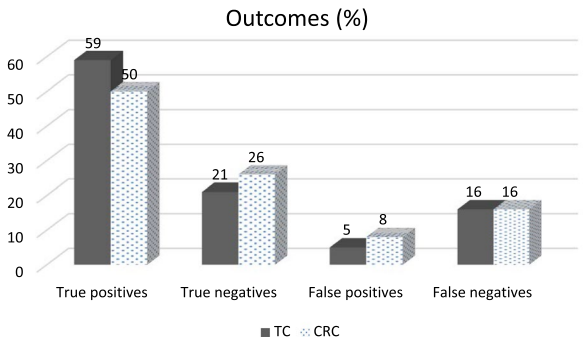

Fig. 1 Outcomes: true positive (TP), true negative (TN), false positive (FP), and false negative (FN) for unresectable advanced thoracic (TC) and colorectal cancer (CRC)

Moreover, the positive predictive value was 92% for thoracic cancer and 87% for colorectal cancer, while the negative predictive value was 56% for thoracic cancer and 61% for colorectal cancer. The AUC for thoracic cancer was 0.84 (95% confidence interval (CI), 0.78–0.89) and 0.85 (95% CI, 0.80–0.89) for colorectal cancer (Table 2).

Using a cut-off point < 90 for the EF-EORTC-QLQ-C30 as suggested by Snyder et al. [30], the positive predictive value decreases in both the thoracic cancer and the colorectal cancer group (89% and 83%, respectively), while the negative predictive value increases in both (67% and 71%, respectively). Therefore, the use of a cut-off point < 75 appears to perform better than < 90.

Discussion

This study demonstrates that the EF-EORTC-QLQ-C30 subscale is a simple and effective tool to detect psychological distress in patients with advanced cancer showing an accuracy of 79% and 76% for subjects with thoracic and colorectal cancer, respectively.

These results confirm not only the utility of this tool but also the high incidence of psychological distress in this population and therefore the need for routine assessment to better diagnose and care for these individuals [9–11]. In fact, HRQoL assessment has been common practice in many clinical trials for years, and emotional functioning is a domain included in most HRQoL measures [29]. Currently, several international guidelines recommend the use of brief screening measures to detect and manage psychological distress in cancer patients [20, 36, 37]. While there are validated scales to measure this parameter, most of them are complex and difficult to apply, and a quick and simple scale such as EF-EORTC-QLQ-C30 is needed to do so more routinely.

This screening aids in the early detection of psychological distress so that interventions can be implemented sooner and repercussions during the disease can be avoided [8, 15]. The relevance of this derives from the fact that clinically significant levels of depressive symptoms have been associated with poorer survival in cancer patients [38, 39]. Thus, Siwik et al. [38] found that the presence of relevant depressive symptoms correlated with worse survival in lung cancer patients. In addition, emotional distress in this population may entail a poorer prognosis [40] given that, as distress increases, coping deteriorates, adherence to treatment worsens [41, 42], and the risk of disease progression or recurrence increases [43, 44].

This assessment pre- and post-cancer treatment, as recommended by ASCO [45], would enable different profiles of patients with psychological distress to be established according to age, gender, and other characteristics. In two studies of patients receiving antineoplastic treatment, younger individuals (40–55 years) reported more anxiety and depression than patients older than 70 years [45, 46] and women reported more of these symptoms than men [46]. Andersen et al. [47] studied the trajectories of anxiety and/or depression symptoms in patients with stage IV non-small cell lung cancer. Anxious and depressive symptoms decreased significantly over time following diagnosis, and persistence of depression was associated with shorter survival. These studies suggest that psychological distress can be detected and assessed, that it may be reversible, doing so, can hold immediate benefits for emotional well-being on survival in the mid-term,. Therefore, it is worthwhile for the oncologist to have a short and rapid screening tool to evaluate the emotional state of cancer patients and ensure proper interpretation of the scores [35, 37, 48].

The present study reveals how the EF-EORTC-QLQ-C30 (cut-off point < 75) is practical to detect psychological distress quickly in patients with advanced thoracic and colorectal cancer. In our sample, this scale has a sensitivity of 79% and 75% and a specificity of 79% and 77%

Table 2 Detecting psychological distress with the Emotional Function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EF-EORTC-QLQ-C30)

	Unresectable advanced thoracic cancer (n = 283)	Unresectable advanced colorectal cancer (n = 356)
Psychometric properties		
Accuracy	0.791	0.761
Sensitivity	0.790	0.754
Specificity	0.794	0.775
Positive predictive value	0.917	0.868
Negative predictive value	0.568	0.619
Area Under the Curve (AUC)*	0.78–0.89	0.80–0.89

*Relationship between EF-EORTC-QLQ-C30 and Brief Symptom Inventory 18 (BSI-18)

for thoracic and colorectal cancer, respectively, considering the BSI-18 as the gold standard of measurement.

Generally, a cut-off point < 66.78 on the EF-EORTC-QLQ-C30 is used to identify cancer patients with psychological problems in line with the distribution of scores in the general population [22]. Snyder et al. [30] recommend using a score < 90. However, we prefer to apply a score < 75, as scores between 66 and 75 would leave some 30% of individuals misidentified. Giesinger et al. [28] have defined a threshold of 70 points on this scale. Nevertheless, the use of this cut-off point in our sample of cases with unresectable advanced cancer appears to perform worse than the one we propose; i.e., 75. These differences in the choice of cut-off point might be related to different characteristics of the populations analyzed in the studies. Therefore, we believe that, in future studies, it would be compelling to probe the influence of clinical and sociodemographic variables in establishing the cut-off point for this subscale. Similarly, it is important that future studies use clinimetric criteria to ensure that measures are accurate, valid, sensitive to change, and useful to assess patients' experiences and tracking their progress over time [49].

The strengths of this study are its large sample size (639 patients), the representativeness of the sample (cases from 15 hospitals throughout Spain), and the fact that the incidence of emotional distress was found in a specific population of patients with unresectable (incurable) advanced cancer at a specific time, following diagnosis and prior to initiating systemic treatment. The incidence was 71–75% in patients with unresectable advanced thoracic and colorectal cancer, similar to figures reported in other series, thereby highlighting the relevance of this issue [48, 50]. This study also has limitations that should be considered. First, its cross-sectional nature. The evaluation was performed before starting antineoplastic treatment; consequently, there may be patients who emotionally adapt to this situation during treatment and others who, on the contrary, get worse. Therefore, for the future, it would be important to assess whether the EF-EORTC-QLQ-C30 scale is also useful to detect emotional distress during and after cancer treatment. Second, the psychometric properties and sensitivity of the EF-EORTC-QLQ-C30 were adequate to detect psychological distress in cancer patients; consequently, the cut-off point used in this research should be validated in patients with other types of cancer and at other stages. Third, the reference test was another questionnaire, the BSI-18, and no psychiatric assessment or clinical diagnosis was made.

In conclusion, the EF-EORTC-QLQ-C30 was 79% and 76% accurate in detecting psychological distress in patients with advanced thoracic and colorectal cancer, respectively. Therefore, this short, useful scale, with an accurate cut-off point, can help healthcare professionals identify individuals with emotional problems requiring specialized care. The brevity of this scale makes it ideal for longitudinal administration, comparison of results from different studies and analysis of the impact of different treatments and interventions.

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Author contributions
ARG, PJF, and CC contributed equally to this work and coordinated the project. They conducted the database search, screened, extracted the data, and wrote the first draft. All authors have made substantial contributions to the conception of the work, data collection, analysis, interpretation of data, and approved the final version to be published. All authors read and approved the final manuscript.

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Data availability
The datasets generated and analyzed during the current study are not publicly available for reasons of privacy. They are, however, available (fully anonymized) from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participant
The study was approved by the Research Ethics Committee of the Principality of Asturias (May 17, 2019) and by the Spanish Agency of Medicines and Medical Devices (AEMPS) (identification code: L34LM-MM2GH-Y925U-RJDHQ). The study and all procedures have been performed in accordance with the ethical standards of the National Research Committee and the 1964 Declaration of Helsinki and its subsequent amendments. The study is an observational, non-interventionist trial. Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interest
The authors declare that they have no competing interest.

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Publisher's Note

INFORME DE FACTOR DE IMPACTO

Artículo 1:

Revista: Current Oncology, ISSN 1198-0052, EISSN 1718-7729. Edition: Science Citation Index Expanded (SCIE). Category: Oncology-SCIE. Languages: English. Región: Switzerland. 1ST Electronic JCR year: 2010.

JOURNAL IMPACT FACTOR: 3.109

Artículo 2:

Revista: International Journal of Environmental Research and Public Health, EISSN 1660-4601. Edition: Social Sciences Citation Index (SSCI), Science Citation Index Expanded (SCIE). Category: Public, environmental & occupational health - SSCI. Languages: English. Región: Switzerland. 1ST Electronic JCR year: 2011

JOURNAL IMPACT FACTOR: 4.614

Artículo 3:

Revista: ONCOLOGIST, ISSN 1083-7159, EISSN 1549-490X. Edition: Science Citation Index Expanded (SCIE). Category: Oncology-SCIE. Languages: English. Región: USA. 1ST Electronic JCR year: 2003

JOURNAL IMPACT FACTOR: 5.837

Articulo 4:

Revista: Clinical & Translational Oncology, ISSN 1699-048X, EISSN 1699-3055. Edition: Science Citation Index Expanded (SCIE). Category: Oncology-SCIE. Languages: English. Región: Spain. 1ST Electronic JCR year: 2009

JOURNAL IMPACT FACTOR: 3.340

Artículo 5:

Revista: Health and Quality of Life Outcomes, EISSN 1477-7525. Edition: Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI). Category: Health policy & services – SSCI, Health care sciences & services - SCIE. Languages: English. Región: England. 1ST Electronic JCR year: 2008

JOURNAL IMPACT FACTOR: 3.007

ESTUDIO NEOETIC: 'Evaluación de la toma de decisiones, expectativas y afrontamiento en pacientes con cáncer avanzado'

HOJA DE INFORMACIÓN AL PACIENTE

Título: ESTUDIO NEOETIC: 'Evaluación de la toma de decisiones, expectativas y afrontamiento en pacientes con cáncer avanzado'. **Código: No-EPA-NEOetic-v1**

Promotor: Grupo de Bioética de la Sociedad Española de Oncología Médica (SEOM)
Equipo coordinador: 1) Dra. Paula Jiménez Fonseca. Oncóloga médica. Hospital Universitario Central de Asturias, Oviedo. 2) Dra. Caterina Calderón. Psicóloga Clínica. Psicología Clínica y Psicobiología. Facultad de Psicología. Universidad de Barcelona, Barcelona. 3) Dr Alberto Carmona-Bayonas. Oncólogo médico. Hospital Universitario Morales Meseguer, Universidad de Murcia, Murcia. 4) Dra Teresa García García. Oncóloga médica. Hospital General Universitario Santa Lucia, Cartagena, Murcia.
En el Servicio de Oncología Médica del hospital…….. se está realizando un estudio en el que se le invita a participar después de que haya leído la información que se le facilita en estas páginas, y haya consultado y aclarado todas las dudas. Pregunte a su médico cualquier cuestión, y solicítele cualquier aclaración que considere necesaria, para que pueda decidir de forma libre y con la información necesaria, si quiere o no participar en este estudio.

Pacientes participantes en el estudio. Se prevé una participación de entre 416 y 1248 pacientes.

Procedimientos. Recogida de datos de pacientes con un cáncer avanzado.

Finalidad del estudio. Se evaluarán las estrategias de afrontamiento de la enfermedad, la toma de decisión compartida entre paciente y médico, los síntomas psicológicos, la calidad de vida y las expectativas de los pacientes. Además, se correlacionarán con datos psicosociales y clínicos.

Beneficios y riesgos de la participación en el estudio. Usted será tratado según la práctica clínica habitual de su médico. No existen beneficios específicos relacionados con su participación, ni tampoco tendrá un riesgo adicional diferente al que de por sí tiene su enfermedad. El beneficio del estudio proviene de la obtención de datos que completarán el conocimiento de su enfermedad. Este hecho podrá ser usado por la comunidad científica y médica, para establecer nuevas investigaciones, nuevas formas de abordaje psicosocial y de comunicación, que redundará, finalmente, en una mejora asistencial de los pacientes y en la ayuda para afrontar la enfermedad.

Carácter voluntario de la participación. Si decide participar en este estudio se le pedirá que firme un formulario de consentimiento escrito. Si después de pensarlo, decide no participar en el estudio, o una vez que está participando posteriormente cambia de idea, por favor, informe a su médico. Es usted quien tiene que decidir libremente si participar o no, y su médico no tomará partido respecto a su decisión, ni la juzgará. Su participación, por tanto, es de carácter voluntario y si decide retirarse del estudio no se alterará su relación con los médicos, ni se producirá ningún perjuicio en su seguimiento clínico ni en su tratamiento. También el promotor podrá terminar el estudio, durante el desarrollo del mismo.
Confidencialidad de los datos personales. Toda la información relativa al paciente será tratada de forma estrictamente confidencial. El paciente sólo será identificado por un número. El tratamiento de los datos de carácter personal requeridos en este ensayo se rige por la Ley Orgánica 3/2018, de Protección de Datos de carácter personal, y por el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 (RGPD). Usted puede ejercer el derecho de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio. La información obtenida de este estudio no podrá ser revelada a ninguna persona sin su consentimiento por escrito, excepto a su médico o sus colaboradores, al promotor del estudio o sus representantes, a los coordinadores, a los Comités Éticos de Investigación Clínica de los hospitales donde se esté realizando el estudio y, en el caso de que se requiera, a las autoridades competentes.

En la práctica, la transmisión de la información se hará de forma que no permita identificar al paciente. El médico y sus colaboradores en el estudio transmitirán la información a través de un cuaderno de recogida de datos electrónico al servidor dispuesto para tal fin. Los datos finalmente registrados en la base de datos central serán analizados por el equipo coordinador del estudio. Los resultados obtenidos en este estudio se usarán para presentaciones o publicaciones científicas. En el caso de que los resultados de este estudio se publicasen, el nombre del paciente no será nunca mencionado. En dichas publicaciones o presentaciones se mantendrá la confidencialidad de los datos, de acuerdo con el Reglamento General de Protección de Datos (RGPD).

Debe saber que este estudio ha sido aprobado por el Comité de Ética de la Investigación con Medicamentos del Principado de Asturias, comité de referencia y que se realizará cumpliendo la legislación europea y española vigente para este tipo de estudios.

Persona de contacto. Durante todo el estudio podrá formular cualquier pregunta que tenga a su médico. Si surge algún problema o más preguntas sobre el estudio, póngase en contacto con la persona indicada a continuación:

Nombre: ……

Dirección: …….. Teléfono: ……

CONSENTIMIENTO INFORMADO

Título: ESTUDIO NEOETIC: 'Evaluación de la toma de decisiones, expectativas y afrontamiento en pacientes con cáncer avanzado'.

Yo ……..
(nombre y apellidos del paciente)
He recibido la información contenida en la hoja de información al paciente sobre el estudio.
He podido hacer las preguntas necesarias y he recibido suficiente información sobre el estudio.

- He hablado con el doctor …….....

Comprendo que mi decisión sobre la participación en el estudio es voluntaria.
Comprendo que puedo retirarme del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en sus cuidados médicos.

Entiendo que, al acceder a participar en este estudio, consiento en la recogida, tratamiento, cesión y transferencia (si procede) de mis datos personales, clínicos y la información recogida en los cuestionarios que he cumplimentado, con respeto del anonimato para fines de atención sanitaria y/o investigación médica.
Presto libremente mi conformidad para participar en el estudio y que mis datos puedan ser utilizados con fines de investigación.
Recibiré una copia firmada de la hoja de información y del consentimiento informado.
Firma del paciente:

Fecha _____/_____/_____

Nombre y apellidos del investigador (en mayúsculas)

……
Firma del investigador:

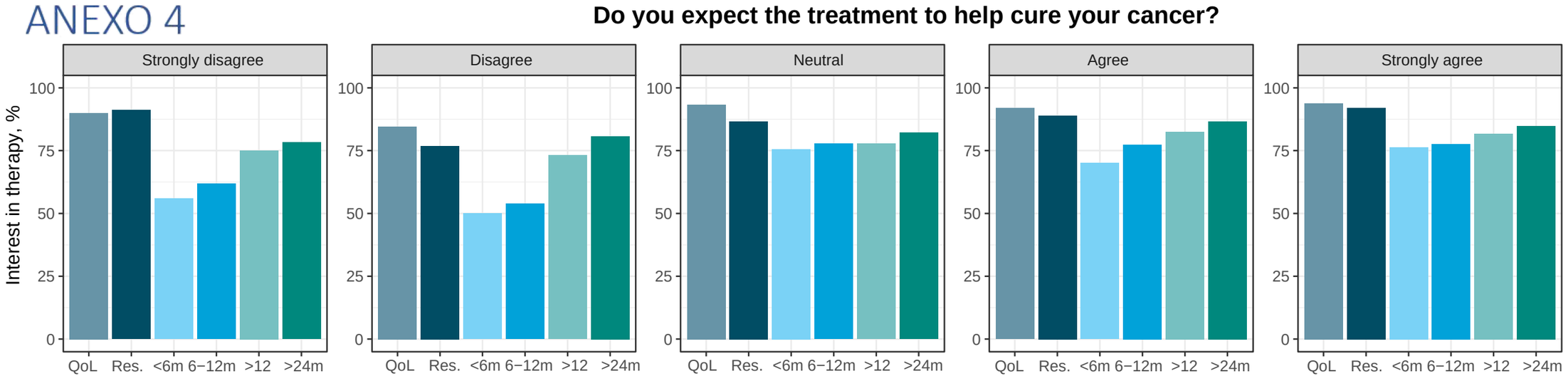
Fecha _____/_____/_____

REVOCACIÓN DEL CONSENTIMIENTO
Firma del paciente:

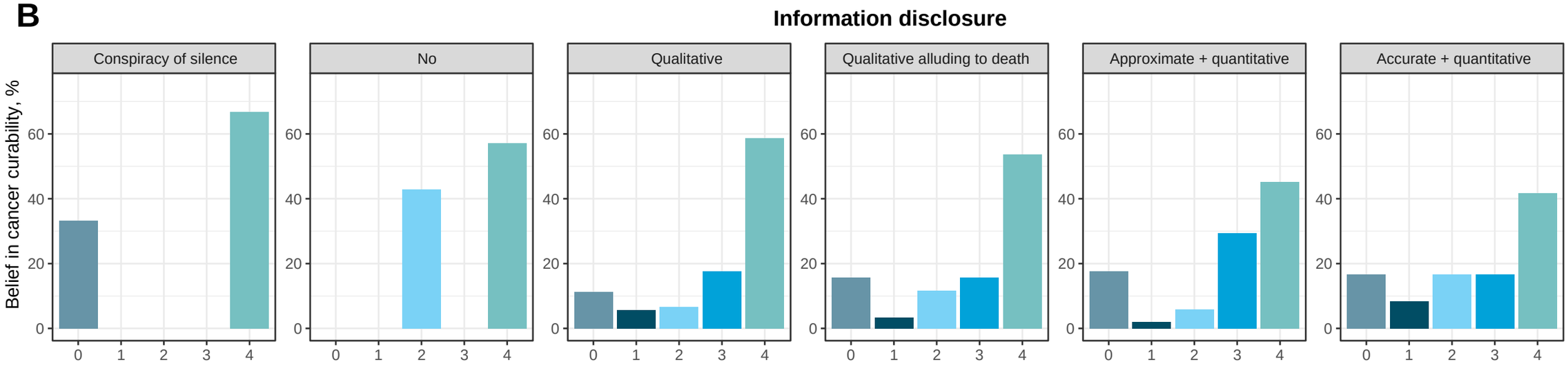
Fecha _____/_____/_____

A

ANEXO 4


Do you expect the treatment to help cure your cancer?
Strongly disagree
Disagree
Neutral
Agree
Strongly agree
Interest in therapy, %
0
25
50
75
100
QoL
Res.
<6m
6−12m
>12
>24m
Scenario
QoL
Res.
<6 m
6−12m
>12m
>24m

B

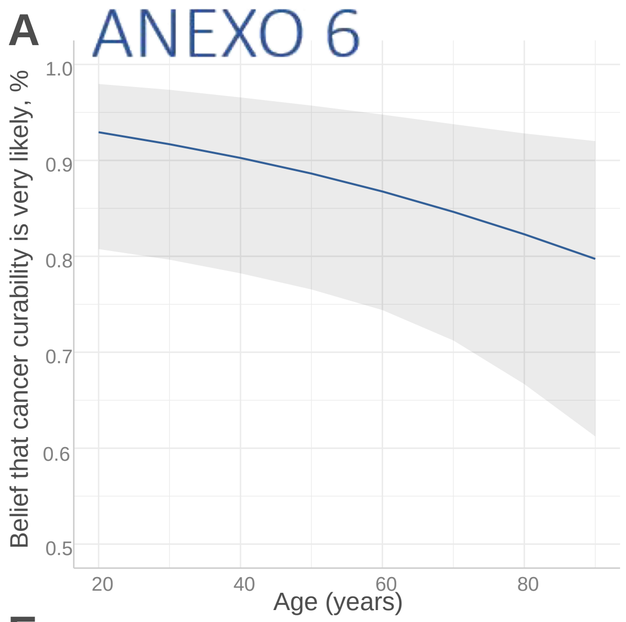

Information disclosure
Conspiracy of silence
No
Qualitative
Qualitative alluding to death
Approximate + quantitative
Accurate + quantitative
Belief in cancer curability, %
0
20
40
60
0
1
2
3
4
Belief in curability
0 Strongly disagree
1 Disagree
2 Neutral
3 Agree
4 Strongly agree

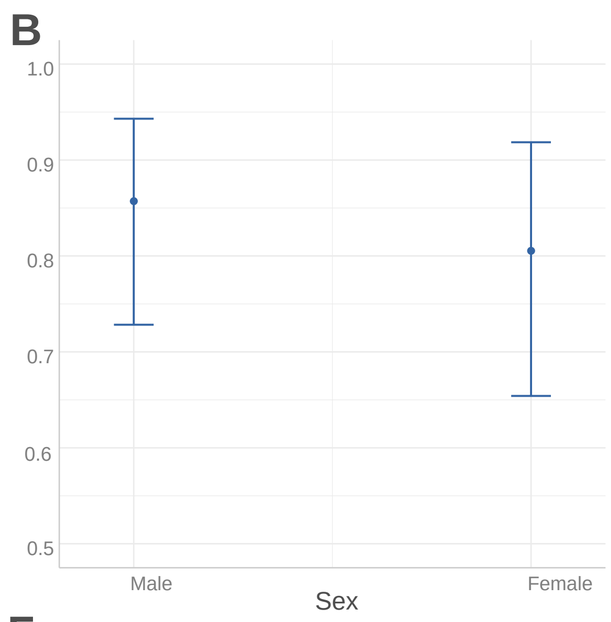
ANEXO 5

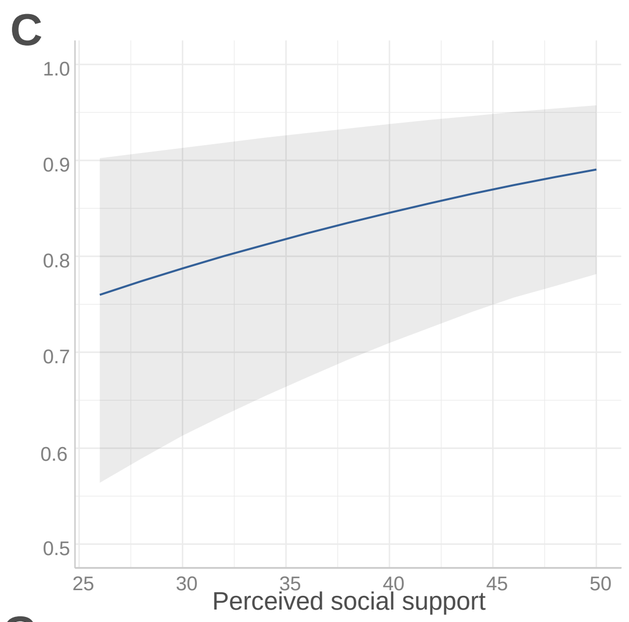
Tabla 2. Regresión ordinal para 'creencia en la curabilidad del cáncer'

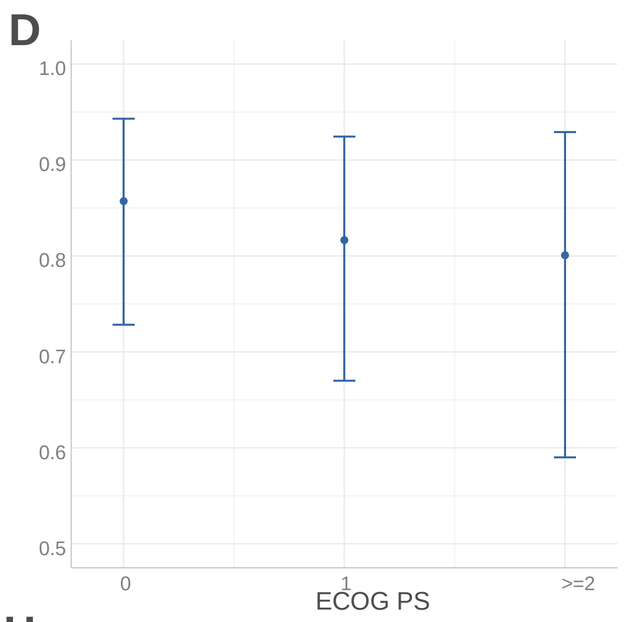
Population-level effects (β)	**Estimate (95%, HDI)**	**i-95% HDI**	**u-95% HDI**	**ESS**
Intercept[1]	-2.79	-4.72	-0.94	11585
Intercept[2]	-2.37	-4.31	-0.52	11653
Intercept[3]	-1.79	-3.70	0.05	11822
Intercept[4]	-0.82	-2.73	1.02	11965
Age	-0.02	-0.03	-0.00	16790
Sex, female	-0.37	-0.75	0.02	16028
Expected survival	0.02	0.00	0.03	13704
Immunetherapy	-0.01	-0.53	0.51	14907
Targetted therapy	-0.22	-0.70	0.27	12674
QLQ-C30 symptoms scales	-0.01	-0.02	0.00	15979
Perceived social support	0.04	0.02	0.06	16574
Spirituality	0.02	0.00	0.03	16572
Lung cancer	-0.08	-0.64	0.48	9563
H&N	-0.28	-4.07	3.43	17079
Upper GI	-0.54	-1.13	0.04	10077
Breast	-1.80	-2.65	-0.97	13785
Others	-0.36	-1.05	0.33	11614
ECOG PS				
0	Ref.	Ref.	Ref.	-
1	-0.30	-0.71	0.11	13402
2	-0.41	-1.15	0.36	14182
Oncological setting (mo)	0.12	-0.04	0.30	11442
Information disclosure (mo)	-0.23	-0.49	-0.01	7410
Fear of death (mo)	-0.23	-0.40	-0.07	10402
Simplex parameters (ζ)				
Oncological setting [ζ1]	0.28	0.01	0.73	14427
Oncological setting [ζ2]	0.20	0.01	0.64	13219
Oncological setting [ζ3]	0.26	0.01	0.71	14295
Oncological setting [ζ4]	0.26	0.01	0.70	11806
Information disclosure [ζ1]	0.16	0.01	0.50	9703
Information disclosure [ζ2]	0.14	0.00	0.45	12989
Information disclosure [ζ3]	0.22	0.01	0.56	9529
Information disclosure [ζ4]	0.23	0.01	0.60	11663
Information disclosure [ζ5]	0.25	0.01	0.64	12341
Fear of death [ζ1]	0.64	0.14	0.94	11257
Fear of death [ζ2]	0.25	0.01	0.71	11640
Fear of death [ζ3]	0.11	0.00	0.40	13278

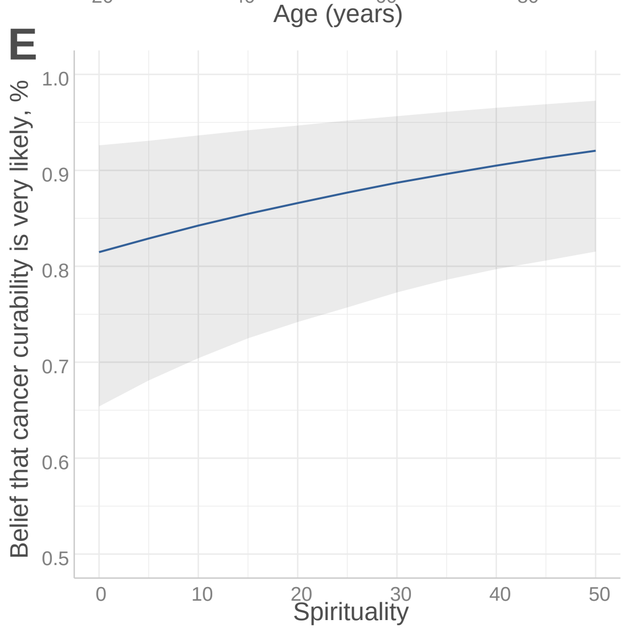
ANEXO 6

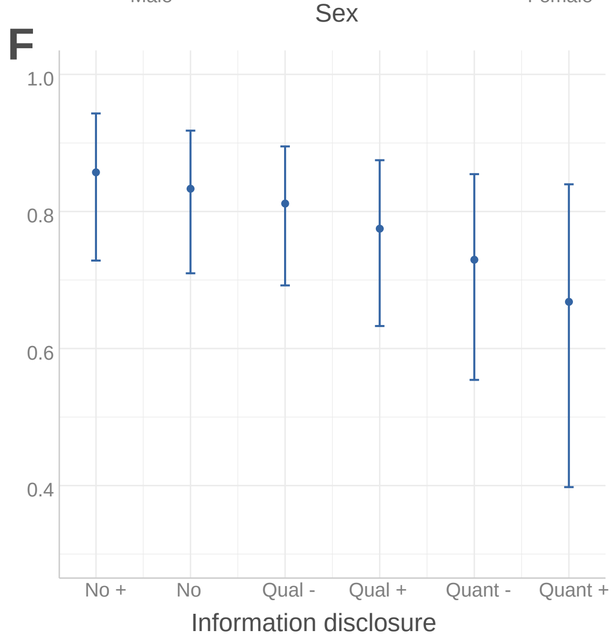

A
Belief that cancer curability is very likely, %
1.0
0.9
0.8
0.7
0.6
0.5
20
40
60
80
Age (years)

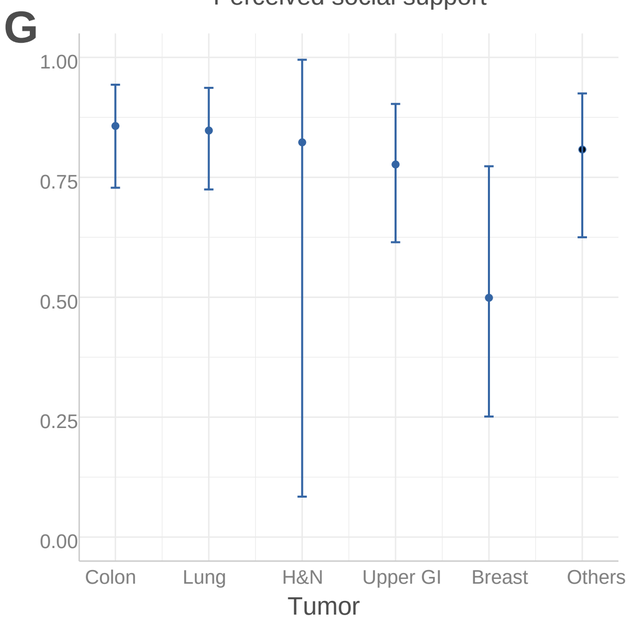

B
1.0
0.9
0.8
0.7
0.6
0.5
Male
Female
Sex

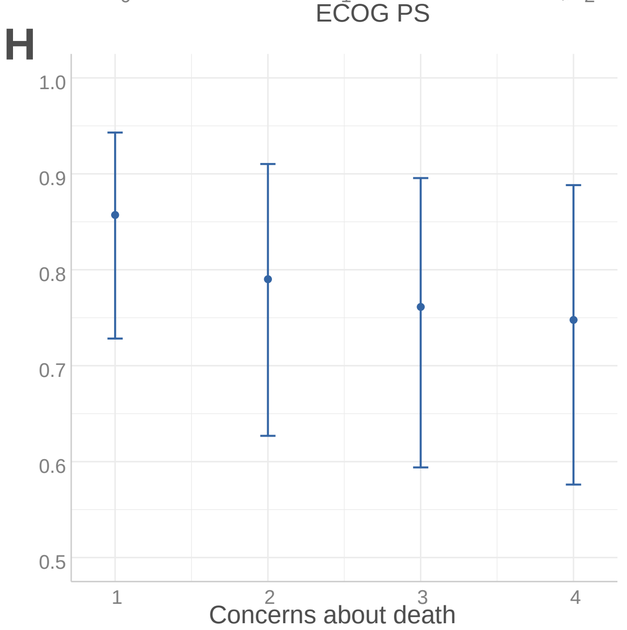

C
1.0
0.9
0.8
0.7
0.6
0.5
25
30
35
40
45
50
Perceived social support

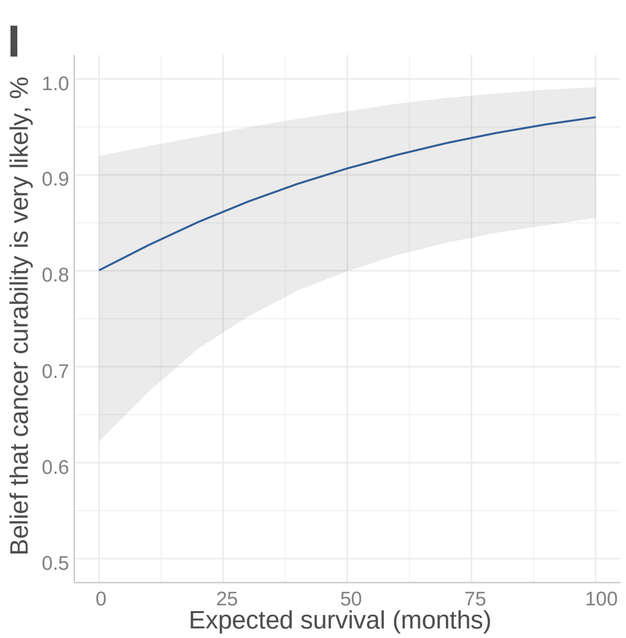

D
1.0
0.9
0.8
0.7
0.6
0.5
0
1
>=2
ECOG PS

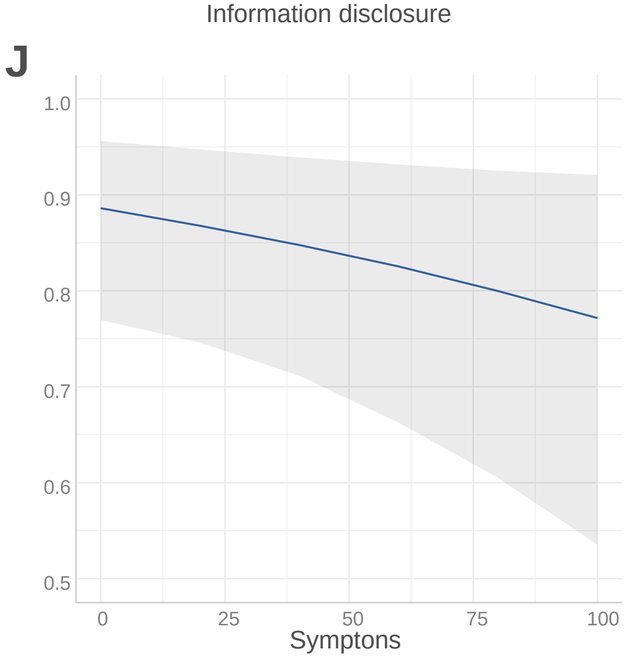

E
Belief that cancer curability is very likely, %
1.0
0.9
0.8
0.7
0.6
0.5
0
10
20
30
40
50
Spirituality

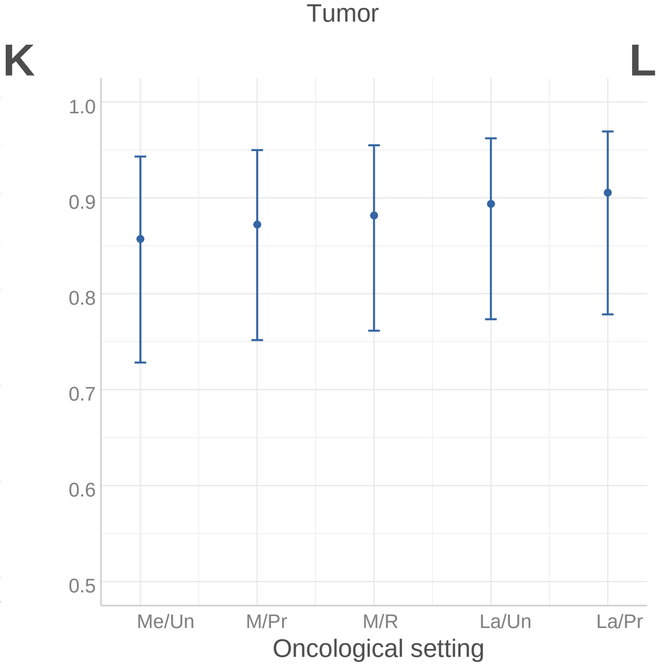

F
1.0
0.8
0.6
0.4
No +
No
Qual -
Qual +
Quant -
Quant +
Information disclosure

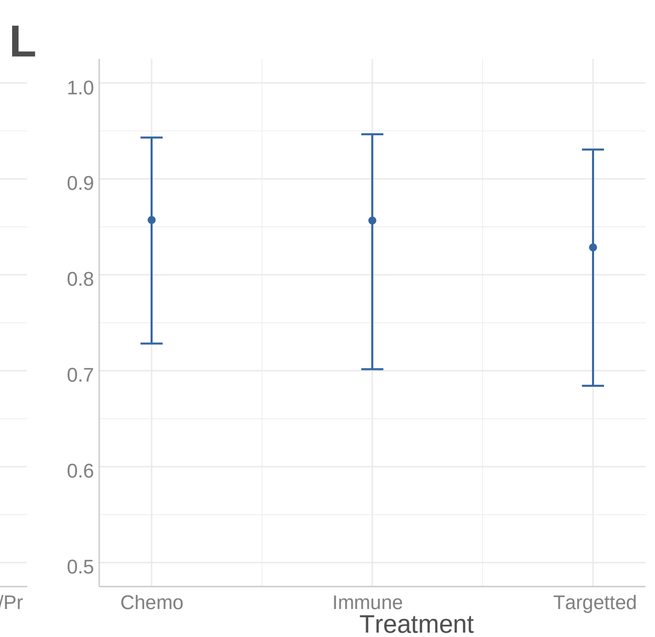

G
1.00
0.75
0.50
0.25
0.00
Colon
Lung
H&N
Upper GI
Breast
Others
Tumor


H
1.0
0.9
0.8
0.7
0.6
0.5
1
2
3
4
Concerns about death


I
Belief that cancer curability is very likely, %
1.0
0.9
0.8
0.7
0.6
0.5
0
25
50
75
100
Expected survival (months)


J
1.0
0.9
0.8
0.7
0.6
0.5
0
25
50
75
100
Symptons


K
1.0
0.9
0.8
0.7
0.6
0.5
Me/Un
M/Pr
M/R
La/Un
La/Pr
Oncological setting

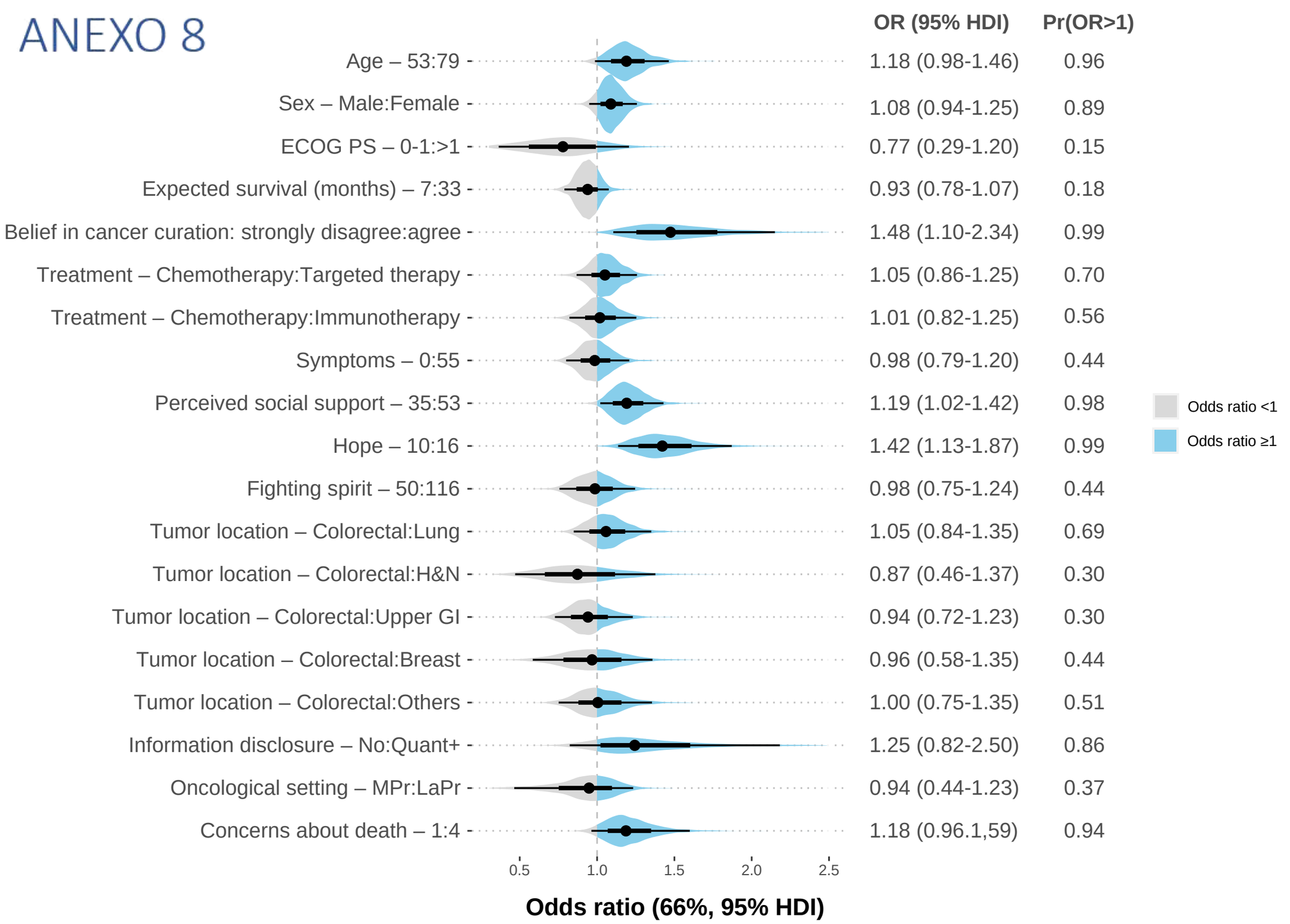

L
1.0
0.9
0.8
0.7
0.6
0.5
Chemo
Immune
Targetted
Treatment

ANEXO 7

Tabla 3. Regresión ordinal para 'interés en terapias con mejora OS <6 meses'

Population-level effects (β)	**Estimate (95%, CreI)**	**l-95% CreI**	**u-95% CrI**	**ESS**
Intercept[1]	1.10	-2.34	4.35	8837
Intercept[2]	1.52	-1.93	4.76	8829
Intercept[3]	2.16	-1.26	5.40	8823
Intercept[4]	2.74	-0.67	5.98	8818
Age' (ns)	-1.66	-7.28	3.13	10199
Age'' (ns)	0.76	-0.33	1.84	9846
Sex, female	0.24	-0.14	0.63	12431
Expected survival	0.01	-0.02	0.01	10080
Inmunotherapy	0.05	-0.48	0.59	11997
Targetted therapy	0.14	-0.34	0.62	9728
QLQ-C30 symptoms scales	-0.00	-0.01	0.01	13874
Perceived social support	0.03	0.00	0.05	13805
Fighting spirit	-0.00	-0.01	0.01	11755
Hope	0.15	0.06	0.25	11515
Lung cancer	0.15	-0.41	0.69	6500
H&N	-0.27	-1.37	0.85	9400
Digestive non-colorectal	-0.13	-0.72	0.46	6291
Breast	-0.06	-0.98	0.86	9370
Others	0.04	-0.62	0.73	8268
ECOG PS, >1	-0.38	-1.07	0.32	13249
Oncological setting (mo)	-0.05	-0.36	0.13	5899
Information disclosure (mo)	0.15	-0.10	0.47	5383
Fear of death (mo)	0.12	-0.03	0.27	10386
Belief in cancer curability (mo)	0.19	0.05	0.32	9088
Simplex parameters (ζ)				
Oncological setting [ζ1]	0.21	0.01	0.66	9010
Oncological setting [ζ2]	0.21	0.01	0.67	9564
Oncological setting [ζ3]	0.22	0.01	0.69	9778
Oncological setting [ζ4]	0.36	0.01	0.87	5533
Information disclosure [ζ1]	0.23	0.01	0.64	11230
Information disclosure [ζ2]	0.22	0.01	0.62	10013
Information disclosure [ζ3]	0.14	0.00	0.48	8850
Information disclosure [ζ4]	0.17	0.00	0.54	10665
Information disclosure [ζ5]	0.24	0.01	0.64	8960
Fear of death [ζ1]	0.26	0.01	0.74	11289
Fear of death [ζ2]	0.44	0.03	0.89	10847
Fear of death [ζ3]	0.30	0.01	0.79	11384
Belief in cancer curability [ζ1]	0.24	0.01	0.66	11218
Belief in cancer curability [ζ2]	0.30	0.02	0.72	9980
Belief in cancer curability [ζ3]	0.19	0.01	0.57	12558
Belief in cancer curability [ζ4]	0.28	0.01	0.66	10078

ANEXO 8


OR (95% HDI)
Pr(OR>1)
Age – 53:79
1.18 (0.98-1.46)
0.96
Sex – Male:Female
1.08 (0.94-1.25)
0.89
ECOG PS – 0-1:>1
0.77 (0.29-1.20)
0.15
Expected survival (months) – 7:33
0.93 (0.78-1.07)
0.18
Belief in cancer curation: strongly disagree:agree
1.48 (1.10-2.34)
0.99
Treatment – Chemotherapy:Targeted therapy
1.05 (0.86-1.25)
0.70
Treatment – Chemotherapy:Immunotherapy
1.01 (0.82-1.25)
0.56
Symptoms – 0:55
0.98 (0.79-1.20)
0.44
Perceived social support – 35:53
1.19 (1.02-1.42)
0.98
Hope – 10:16
1.42 (1.13-1.87)
0.99
Fighting spirit – 50:116
0.98 (0.75-1.24)
0.44
Tumor location – Colorectal:Lung
1.05 (0.84-1.35)
0.69
Tumor location – Colorectal:H&N
0.87 (0.46-1.37)
0.30
Tumor location – Colorectal:Upper GI
0.94 (0.72-1.23)
0.30
Tumor location – Colorectal:Breast
0.96 (0.58-1.35)
0.44
Tumor location – Colorectal:Others
1.00 (0.75-1.35)
0.51
Information disclosure – No:Quant+
1.25 (0.82-2.50)
0.86
Oncological setting – MPr:LaPr
0.94 (0.44-1.23)
0.37
Concerns about death – 1:4
1.18 (0.96.1,59)
0.94
Odds ratio <1
Odds ratio ≥1
0.5
1.0
1.5
2.0
2.5
Odds ratio (66%, 95% HDI)