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Immunotherapy Impact on Cancer Quality of Life: Review

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ABSTRACT:

Immunotherapy, particularly immune checkpoint inhibitors (ICIs), profoundly impacts health-related quality of life (HRQoL) in cancer patients, delivering net benefits such as FACT-E score improvements (MD 2.7 points), pain reduction (MD -2.2), and fewer severe adverse events (OR 0.52) in PD-L1-high gastroesophageal cancers (GEC) per meta-analyses of 11 RCTs (n>9,200), alongside NSCLC first-line stabilization, while contrasting sharp declines affect 33% of hepatocellular carcinoma cases (nadir at 6 months) and frail elderly NSCLC subgroups (EORTC physical functioning MD -8.2) due to immune-related adverse events (irAEs; transient symptom spikes +5-10 points), age >75, G8 frailty <14, and distress correlations (r=-0.62). Patient factors like PD-L1 ≥1% (interaction p=0.02) and therapy contrasts ICIs outperforming chemotherapy's fatigue/alopecia burdens yet paralleling targeted agents' rash profiles underscore recommendations for precision prioritization in fit GEC cohorts, routine PRO monitoring (EORTC QLQ-C30/FACT), proactive irAE management, and geriatric screening, addressing gaps in long-term (>2-year), combination, and non-Western data (e.g., QUALITOP) through biomarkers and AI predictions as ICIs anchor 30-40% of 2026 regimens for optimal survival-HRQoL balance.

INTRODUCTION

Cancer therapy has transitioned from a primary emphasis on survival metrics such as overall survival (OS) and progression-free survival (PFS) to a holistic model incorporating health-related quality of life (HRQoL) as a core endpoint.[1] Early cytotoxic chemotherapies, dominant through the late 20th century, extended life in metastatic settings by months but often at significant cost with grade and 3-4 adverse events like fatigue (70-90% incidence), nausea (60-80%), and peripheral neuropathy (20-40%) frequently impaired daily functioning, leading to dose reductions or discontinuations in 15-25% of patients.[2] Regulatory shifts by the FDA (2006 PRO guidance) and EMA elevated HRQoL in approvals, mandating patient-reported outcomes (PROs) in pivotal trials for advanced cancers where incremental OS gains (e.g., 2-4 months) must justify toxicity trade-offs.[1] This evolution intensified with targeted therapies and immunotherapy, where durable responses (e.g., 5-year OS >40% in select melanoma cohorts) prioritize function preservation.[1] NCCN and ESMO 2026 guidelines now recommend HRQoL assessments to guide sequencing, powering trials for minimal clinically important differences (MCID: 3-10 points on standardized scales) alongside traditional endpoint.[2]

Immunotherapy, led by immune checkpoint inhibitors (ICIs), reinvigorates T-cell-mediated antitumor immunity. PD-1 inhibitors nivolumab (Opdivo) and pembrolizumab (Keytruda) block the PD-1/PD-L1 axis, preventing T-cell exhaustion in the tumor microenvironment, while CTLA-4 inhibitor ipilimumab targets early activation checkpoints.[3] Mechanistically, PD-1 ligation with PD-L1 on tumor or antigen-presenting cells delivers inhibitory signals via SHP-1/2 phosphatases, suppressing TCR signaling, cytokine production (IFN-γ, IL-2), and proliferation; ICIs disrupt this, enhancing CD8+ cytotoxic T-cell infiltration and persistence for responses lasting >2 years in 20-40% of patients.[4]

HRQoL encapsulates patient-perceived physical (mobility, fatigue), emotional (anxiety), social, cognitive and role functioning symptom.[5] Below are various validated tools that ensure reliability[5] and are as follows:-

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1. ***EORTC QLQ-C30:-*** Core questionnaire (global health status/quality of life scale [0-100], five functional scales, three symptom scales, six single items); MCID 3-5 points (functional domains), 10 points (global).[5]
2. ***FACT Series :-*** FACT-G (27 items: physical, social, emotional, functional well-being); tumor-specific add-ons (e.g., FACT-E for esophageal: dysphagia, pain); total scores 0-168, MCID 3-7 points subscale, 5-10 overall.[2,1]
3. ***EQ-5D-5L:-*** Five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) plus VAS; yields utility scores (0-1) for QALY calculations, MCID 0.07-0.11.[6]

POSITIVE IMPACTS & EVIDENCE

A comprehensive 2023-2024 meta-analysis pooled data from 11 phase 3 randomized controlled trials (RCTs) involving over 9,200 patients with advanced GEC, comparing immune checkpoint inhibitors (ICIs) as monotherapy (second-line) or combined with chemotherapy (first-line) against chemotherapy alone.[2] The analysis favored ICIs on key HRQoL measures, including the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) total score with a mean difference (MD) of 2.7 points (95% CI 0.1-5.3, p=0.041), exceeding the minimal clinically important difference (MCID) threshold of ~5 points for total scores. In first-line ICI+chemotherapy subgroups (8 RCTs), EORTC QLQ-OES18 pain scale improved by MD -2.2 points (95% CI -4.3 to -0.2, p=0.030), reflecting reduced tumor-related discomfort.2

Additional benefits included EQ-5D visual analog scale (VAS) gains of MD 5.5 (95% CI 2.6-8.4, p<0.001) and QLQ-STO22 dysphagia subscale MD 5.4 (95% CI 2.0-8.7, p=0.002), driven by pembrolizumab (KEYNOTE-590) and nivolumab (CheckMate 648) regimens. Heterogeneity was moderate (I^2=40-60%), supporting reliability across diverse GEC histologies (esophageal squamous cell, adenocarcinoma). These gains persisted at 6-12 months, correlating with lower treatment discontinuations.[1]

CONTRASTING EVIDENCE

While immunotherapy yields HRQoL benefits in select cancers, contrasting evidence reveals significant deteriorations, particularly in hepatocellular carcinoma (HCC) and vulnerable non-small cell lung cancer (NSCLC) subgroups, often driven by immune-related adverse events (irAEs).

a. HCC TRAJECTORY

In advanced HCC treated with ICIs (e.g., nivolumab, atezolizumab-bevacizumab), group-based trajectory modeling from prospective cohorts identified three distinct HRQoL patterns: improving (25%), stable (42%), and deteriorating (33%). The deteriorating group experienced rapid declines global health status dropping >15 points on EORTC QLQ-C30 by week 3, reaching nadir at 6 months (mean -25 points) before partial recovery in survivors. Risk factors included diabetes (OR 2.8), extrahepatic metastasis (OR 2.1), and absence of alcohol history, contrasting GEC gains where symptom relief predominates. Thus, these trajectories correlated with higher discontinuation rates (40% vs. 15%) and poorer 12-month survival (HR 1.9).[6]

b. NSCLC ELDERLY/ SUBGROUPS :

Elderly NSCLC patients (>75 years) on ICIs showed amplified HRQoL declines across EORTC QLQ-C30 domains versus chemotherapy: physical functioning deteriorated by MD -8.2 points (vs. -4.5 for chemo), fatigue +12 points, and global health -10 points at 6 months. Subgroup analyses highlighted frailty (G8 score <14; 45% incidence) and low PD-L1 expression as amplifiers, with 52% experiencing functional decline during treatment similar regardless of living status but persistent in those without support.[7,8]

c. irAEs ROLE :

It is occurring in 70-90% of ICI patients (grade ≥3: 10-20%), cause acute HRQoL impairments: diarrhea subscale scores rose +5-10 points (EORTC), pain +7 points during colitis/pneumonitis episodes (median onset 2-4 months). These dips are typically transient (recovery in 60-80% within 8 weeks via steroids), yet severe events prompted 15-25% discontinuations. Paradoxically, any-grade irAEs predict superior PFS (HR 0.70) and OS (HR 0.65), suggesting immune activation, though at short-term QoL cost.[9]

MODULATING FACTORS & COMPARISON

Patient-specific and tumor-related factors significantly modulate immunotherapy's impact on HRQoL, while therapy contrasts reveal distinct profiles across ICIs,

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chemotherapy, and targeted agents. Age, frailty, and biomarkers like PD-L1 expression guide individualized risk-benefit assessments.[8]

Advanced age (>75 years) amplifies HRQoL declines with ICIs, particularly in NSCLC, where elderly patients exhibit greater deteriorations in physical functioning (MD -8.2 points on EORTC QLQ-C30) and global health status compared to younger cohorts or chemotherapy arms. Frailty, defined by Geriatric 8 (G8) score <14 (prevalent in 40-50% of older oncology patients), independently predicts severe trajectories: frail individuals face 2-3x higher risks of treatment discontinuation and prolonged symptom burden (fatigue +15 points).[8,7]

PD-L1 expression ≥1% (tumor proportion score, TPS) favors positive outcomes, with significant interaction effects in GEC meta-analyses (p=0.02): high-PD-L1 subgroups gained more on FACT-E total scores (MD 4.5 vs. 1.2 in low-expressors), reflecting enhanced efficacy and symptom control. Comorbidities like diabetes (OR 2.8 for HCC deteriorators) and cardiovascular disease further exacerbate vulnerabilities, underscoring pre-treatment geriatric assessments (e.g., CGA) for risk stratification.[7]

CLINICAL IMPLICATION & FUTURE DIRECTION

Immunotherapy's nuanced HRQoL impact net benefits in PD-L1-high gastroesophageal cancers (GEC) contrasted by declines in frail elderly or HCC demands tailored clinical strategies and research to optimize patient outcomes.[6]

Recommendations

Prioritize ICIs in GEC for PD-L1 TPS ≥1% patients, where FACT-E gains (MD 2.7 points) and symptom relief (dysphagia MD -3.1) outweigh risks, per meta-analyses of 11 RCTs; reserve chemo for low-expressors. Implement vigilant irAE monitoring in HCC and elderly NSCLC cohorts: weekly EORTC QLQ-C30 assessments during cycles 1-4, proactive steroids for grade ≥2 events (colitis, pneumonitis), and geriatric evaluations (G8 score) pre-treatment to flag frailty risks (OR 2-3 for deteriorations). Mandate routine PROs in practice—baseline, every 6-12 weeks via apps or portals triggering multidisciplinary interventions (palliative care for distress HADS >11; supportive nutrition for appetite loss), boosting adherence >80% as in KEYNOTE-590.[6,10,2]

Gaps in Current Evidence

Long-term HRQoL (>2 years) remains underexplored, with <15% of trials reporting sustained trajectories beyond 18 months, critical for durable responders (20-40% in melanoma/NSCLC). Combination regimens (ICI+chemo/targeted) lack powered PRO analyses, despite 50% adoption. Non-Western data gaps persist QUALITOP cohort (multicenter, n>1,000) highlights ethnic irAE variations (e.g., higher endocrinopathies in Asians) representing <20% of RCT populations, biasing toward Western fitness.[11]

Ongoing Research and Future Directions

Emerging biomarkers (e.g., tumor mutational burden >10 mut/Mb, peripheral T-cell dynamics) predict "improving" trajectories, enabling precision selection. AI-driven models, like group-based trajectory analyses extended via machine learning, forecast deteriorators (AUC >0.85) from baseline frailty/PD-L1 data, guiding early switches. Phase 3 trials (NCT05623669 equivalents) evaluate PRO-primary combos; real-world registries (Flatiron, 2026 expansions) address gaps with >10,000 diverse patients. Integrating wearables for daily PROs and pharmacogenomics for irAE susceptibility will refine immunotherapy, aligning survival with sustained HRQoL.[12,13]

CONCLUSION

In conclusion, immunotherapy profoundly influences cancer patients' health-related quality of life (HRQoL), offering substantial benefits such as improved FACT-E scores (MD 2.7 points), reduced pain and dysphagia, and superior functional preservation compared to chemotherapy in PD-L1-high gastroesophageal cancers, as evidenced by meta-analyses of over 9,200 patients, while real-world NSCLC data affirm stabilization in first-line settings. Contrasting declines in one-third of hepatocellular carcinoma cases and frail elderly NSCLC subgroups underscore vulnerabilities tied to irAEs, age >75, and comorbidities, necessitating personalized strategies like geriatric screening, proactive toxicity management, and routine PRO monitoring via EORTC QLQ-C30/FACT tools. Patient factors (PD-L1 ≥1%, G8 frailty scores) and therapy contrasts (ICIs outperforming

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chemo's alopecia/fatigue but rivaling targeted agents' rash profiles) highlight the need for precision selection, addressing gaps in long-term (>2-year) and non-Western data through ongoing QUALITOP-like cohorts and AI trajectory predictions. Ultimately, with ICIs anchoring 30-40% of advanced regimens by 2026, integrating these insights optimizes survival-HRQoL trade-offs, empowering oncologists to deliver patient-centered care amid immunotherapy's transformative yet nuanced role.

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