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# Prognostic value, clinical relevance, and methodological gaps of tumor burden in neuroendocrine tumors (NETs): a systematic review of phase III randomized trials of medical therapies

Arrivi, G; Rinzivillo, M; Badalamenti, G; Filice, A; Modica, R; Partelli, S; Ricci, C; Rossi, RE; Panzuto, F.

**Corresponding author:**
Francesco Panzuto

francesco.panzuto@uniroma1.it

**Author Affiliation:**
talian Association for Neuroendocrine Tumors.

**ADMINISTRATIVE INFORMATION**

**Support -** talian Association for Neuroendocrine Tumors.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY2025110048

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 November 2025 and was last updated on 17 November 2025.

## INTRODUCTION

**Review question / Objective** The objective was to investigate the definition and application of tumor burden across randomized phase III clinical trials involving patients with well-differentiated NETs evaluating the efficacy of medical therapies (phase III trials conducted and ongoing).

**Condition being studied** The definition and application of tumor burden across randomized phase III clinical trials involving patients with well-differentiated NETs evaluating the efficacy of medical therapies.

## METHODS

**Search strategy** In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), we conducted a comprehensive search of PubMed and ClinicalTrials.gov, updated to June 2025.

Complete search strategy on PubMed:
("neuroendocrine tumours"[All Fields] OR "neuroendocrine tumors"[MeSH Terms] OR ("neuroendocrine"[All Fields] AND "tumors"[All Fields]) OR "neuroendocrine tumors"[All Fields]) AND ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomization"[All Fields] OR "randomized"[All Fields] OR "random"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomise"[All Fields] OR "randomised"[All Fields] OR "randomising"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields]) AND (("phase"[All Fields] OR "phase s"[All Fields] OR "phases"[All Fields]) AND "III"[All Fields])

ClinicalTrials.gov URL:

https://clinicaltrials.gov/search?cond=NeuroendocrineTumors&aggFilters=ages:adultolder,phase:3&limit=25&page=1.

**Participant or population** Patients affected by well-differentiated neuroendocrine tumors (NETs) involved in phase III trials concluded and ongoing, investigating medical therapeutic options - including chemotherapy, targeted therapy, somatostatin analogues (SSA), and peptide receptor radionuclide therapy - for advanced (stage IV) GEP, thoracic (lung and thymic), and unknown primary site NETs.

**Intervention** Exposure of interest was the definition, measurement, and use of tumor burden across phase III randomized clinical trials evaluating medical therapies for advanced well-differentiated neuroendocrine tumors (NETs).
Interventions assessed within the included trials comprised somatostatin analogues, targeted therapies (e.g., everolimus, sunitinib, cabozantinib, surufatinib), peptide receptor radionuclide therapy (PRRT), and cytotoxic chemotherapy.

**Comparator** Comparators consisted of placebo, best supportive care, or alternative active medical treatments as reported in the original phase III randomized clinical trials. The review compared how tumor burden was defined, stratified, or analyzed across different study designs rather than comparing clinical treatments directly.

**Study designs to be included** Published and completed phase III trials and ongoing phase III trials.

**Eligibility criteria** Published and completed phase III trials investigating medical therapeutic options - including chemotherapy, targeted therapy, somatostatin analogues (SSA), and peptide receptor radionuclide therapy - for advanced (stage IV) GEP, thoracic (lung and thymic), and unknown primary site NETs. Additionally, ongoing phase III trials identified through ClinicalTrials.gov were included if an appropriate study design was available. The search was limited to English language.

**Information sources** In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a comprehensive search of PubMed and ClinicalTrials.gov, updated to June 2025. The search strategy is reported above in the specified box.

**Main outcome(s)** Investigation of the definition and application of tumor burden across randomized phase III clinical trials involving patients with well-differentiated NETs evaluating the efficacy of medical therapies (phase III trials conducted and ongoing).

**Quality assessment / Risk of bias analysis** A formal risk-of-bias assessment tool (e.g., Cochrane RoB 2) was not applied, as the objective of the review was methodological and descriptive, focusing on how tumor burden was defined, measured, and incorporated into the design and reporting of phase III randomized clinical trials in advanced neuroendocrine tumors. The review did not evaluate treatment effects or clinical outcomes. Potential sources of bias were instead addressed qualitatively, considering heterogeneity in study design, variability in tumor burden definitions, inconsistencies in reporting of stratification factors, and selective availability of subgroup analyses. No quantitative synthesis was performed.

**Strategy of data synthesis** A structured, descriptive synthesis was performed. Owing to substantial heterogeneity across trials in tumor burden definitions, study populations, endpoints, and analytical approaches, no meta-analysis or quantitative pooling was undertaken. Data were extracted independently by three reviewers using a standardized template, and findings were integrated narratively to summarize how tumor burden was defined, measured, and incorporated into trial design and subgroup analyses.

**Subgroup analysis** No statistical subgroup analyses were performed, as the review did not evaluate treatment effects.

**Sensitivity analysis** This review does not include a quantitative meta-analysis; therefore, no sensitivity analysis will be performed. Any methodological variability or differences between studies will be addressed narratively in the Results section.

**Language restriction** English.

**Country(ies) involved** Italy.

**Keywords** tumor burden; neuroendocrine tumors; NETs; prognosis; survival; metastases.

**Contributions of each author**

Author 1 - Giulia Arrivi.
Email: giulia.arrivi@uniroma1.it
Author 2 - Maria Rinzivillo.
Author 3 - Giuseppe Badalamenti.
Author 4 - Angelina Filice.

Author 5 - Roberta Modica.
Author 6 - Stefano Partelli.
Author 7 - Claudio Ricci.
Author 8 - Roberta Elisa Rossi.
Author 9 - Francesco Panzuto.