Advances in the management of neuroendocrine tumours: Evidence from a systematic review

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Abstract. Neuroendocrine tumours (NETs) are rare, biologically diverse neoplasms with a rising incidence due to improved diagnostics. Their management remains challenging, with multiple therapeutic strategies under evaluation. The present systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Literature searches were conducted across PubMed, Cochrane Library and ScienceDirect between January 2018 and July 2025. Eligible studies included randomized controlled trials, cohort studies and observational analyses involving adult patients with NETs. The primary outcomes were progression-free survival (PFS) and overall survival (OS). A total of 271 studies were screened and 22 met the inclusion criteria. Median PFS across therapies ranged between 2 and 23 months, whereas OS ranged between 9.6 and 60 months, depending on treatment type. Dual checkpoint inhibitors (nivolumab plus ipilimumab) demonstrated durable benefits, with OS time exceeding 55 months in some cohorts, whereas peptide receptor radionuclide therapy (PRRT) achieved a median PFS time of 22.8 months compared with 8.5 months for high-dose octreotide. Furthermore, targeted agents, such as sunitinib and nintedanib, improved PFS to ~11 months, with OS time extending beyond 30 months. Chemotherapy regimens such as CAPTEM yielded a PFS of 7-11 months. In conclusion, the present study revealed that NET therapies show heterogeneous but clinically meaningful benefits. PRRT, targeted therapy and combination regimens were revealed to be associated with the most durable outcomes, whereas immunotherapy demonstrated promise in selected patients. Tailored approaches remain crucial to optimize survival and quality of life of patients.

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Introduction

Neuroendocrine tumours represent a diverse and complex group of neoplasms originating from neuroendocrine cells found throughout the body, predominantly in the GI tract, pancreas, and lungs (1). These tumours are unique in their ability to produce hormones and other bioactive substances, which can lead to various clinical syndromes depending on the type and quantity of hormones secreted (2). Despite being relatively rare, the incidence of NETs has steadily risen over the past few decades, partly due to advancements in diagnostic techniques and heightened clinical awareness (3).

NETs are heterogeneous, both in terms of their biological behaviour and clinical presentation. The overall incidence is estimated to be around 5.86 per 100,000 individuals annually, and it has been increasing over the years (4). This rise in incidence can be attributed to improved imaging techniques, more widespread use of endoscopy, and increased screening practices that lead to the detection of asymptomatic cases (5).

The World Health Organization classifies NETs based on their histopathological characteristics (6). NETs are generally categorized into well-differentiated and poorly differentiated tumours, further classified into grades 1, 2, and 3 based on the Ki-67 index (6). Well-differentiated NETs typically have a low behaviour, whereas poorly differentiated neuroendocrine

carcinomas (NECs) are more aggressive and have poorer prognoses (7).

The pathophysiology of NETs is closely linked to their neuroendocrine origin, which endows them with the ability to secrete a variety of peptides and amines. This leads to distinct clinical syndromes (8). For instance, carcinoid syndrome, often associated with gastrointestinal NETs, results from the secretion of serotonin and other vasoactive substances (9). The genetic underpinnings of NETs are also diverse, with common mutations identified in genes such as MEN1, DAXX, and ATRX, particularly in pNETs (10,11). Mutations in the MEN1 gene, which encodes the protein menin, are frequently observed in familial cases of NETs and are also present in sporadic cases (12). The loss of function of menin leads to unchecked cellular proliferation and tumour formation. Similarly, mutations in DAXX and ATRX, which are involved in chromatin remodelling, have been associated with more aggressive forms of NETs and are considered poor prognostic markers (13).

The clinical presentation of NETs can vary widely depending on the tumour's location, its size, the grade of the tumour, and its functional status. For example, insulinomas, which secrete insulin, can cause recurrent hypoglycaemia, while gastrinomas, which secrete gastrin, lead to Zollinger-Ellison syndrome, characterized by severe peptic ulcers (14). In contrast, non-functional NETs, which do not secrete hormones, may remain asymptomatic for a long time and are often discovered incidentally during imaging studies performed for other reasons (15). When symptoms do occur in these tumours, they are typically related to the tumour's mass effect or metastasis. The liver is the most common site of metastatic spread, particularly in gastrointestinal and pNETs (16).

Therapeutic strategies for neuroendocrine tumours have evolved rapidly alongside advances in pathway-targeted treatments. A significant milestone was reached on 26 March 2025, when the U.S. Food and Drug Administration authorized cabozantinib for patients with unresectable or metastatic pancreatic and extra pancreatic NETs who had progressed after prior systemic therapy (17). In addition, belzutifan, a selective hypoxia-inducible factor-2α inhibitor, was approved for the management of malignant pheochromocytoma and paraganglioma, representing a new metabolism-oriented therapeutic paradigm in neuroendocrine oncology (18).

At the same time, peptide receptor radionuclide therapy continues to advance beyond conventional ^{177}Lu-DOTATATE, with ongoing development of somatostatin receptor antagonists and alpha-particle-emitting radionuclides aimed at improving tumour targeting and cytotoxic efficacy (19). Beyond radionuclide-based approaches, novel immunotherapeutic strategies are emerging as promising avenues that may substantially reshape systemic treatment options for NETs in the near future.

The diagnosis of NETs involves a combination of clinical evaluation, biochemical testing of markers (17,18) and imaging studies, such as CT, MDI and DORATATE PET/CT (19,20). When it comes to histopathological confirmation, the assessment of the Ki-67 index is important in determining the tumour grade and guiding treatment decisions (21,22).

The management of NETs is complex and requires a multidisciplinary approach. Surgical resection remains the cornerstone of treatment for localized NETs and offers the best chance for cure (23). Many patients are admitted to the hospital with advanced or metastatic disease at diagnosis, for which systemic therapies are the core of treatment (24). SSAs such as octreotide and lanreotide are used to control symptoms and slow tumour progression in patients with functional NETs (25). Targeted therapies such as the mammalian target of rapamycin (mTOR) inhibitor everolimus have demonstrated efficacy in treating advanced pNETs, providing both antiproliferative and symptom control effects (26). Similarly, the tyrosine kinase inhibitor sunitinib is approved for treating advanced pNETs and has been shown to improve progression-free survival in this patient population (27).

Despite advances in the understanding and treatment of NETs, several challenges remain. The heterogeneous nature of these tumours poses significant challenges in diagnosis, treatment, and prognosis (28). The rarity of NETs has also limited the ability to conduct large-scale clinical trials, resulting in a reliance on retrospective studies and small, prospective cohorts for much of the available evidence (29). Moreover, while new therapies have improved outcomes for some patients, others continue to experience poor prognosis, particularly those with high-grade or poorly differentiated NETs (30).

Accordingly, this systematic review aimed to evaluate contemporary therapeutic strategies for adult patients with neuroendocrine tumours. Using the PICO framework, the population included adult patients with NETs; interventions comprised surgery, systemic therapies, targeted agents, immunotherapy, and peptide receptor radionuclide therapy; comparators included alternative treatment strategies or standard of care where applicable; and outcomes of interest were progression-free survival, overall survival, and treatment-related outcomes.

Materials and methods

Study design. This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which ensure a rigorous and transparent approach to synthesizing evidence from the literature (31). This review evaluated the efficacy and safety of various treatment modalities for NETs, including surgery, chemotherapy, targeted therapy, and PRRT. The review was not prospectively registered in the PROSPERO database as the study was designed as an exploratory synthesis of recently emerging therapeutic strategies in neuroendocrine tumours, and the review process was initiated prior to protocol registration. Nevertheless, all methodological steps, including eligibility criteria, search strategy, study selection, data extraction, and synthesis methods, were predefined and consistently applied throughout the review.

Eligibility criteria. This review included randomized controlled trials (RCTs), cohort studies, and observational studies. Only studies published in peer-reviewed journals were considered, and prospective and retrospective studies were included. Systematic reviews and meta-analyses were used for

reference and comparison but were not part of the primary analysis.

PICO framework (32,33):

i) Participants: Eligible studies involved adult patients (aged 18 years and older) diagnosed with neuroendocrine tumours, regardless of tumour location (e.g., gastrointestinal, pancreatic, pulmonary NETs) or grade (well-differentiated or poorly differentiated). Studies involving paediatric populations or animal models were excluded.

ii) Interventions: The review focused on therapeutic interventions for NETs, including, but not limited to, surgical interventions, chemotherapy (both single-agent and combination regimens), targeted therapies (including mTOR inhibitors, e.g., everolimus and tyrosine kinase inhibitors, e.g., sunitinib), and PRRT.

iii) Comparison: Evaluating different treatment plans.

iv) Outcomes: The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS).

Only studies published in English were included in this review. To ensure the relevance of findings to current clinical practices, the search timeframe was January 2019 to July 2025.

Information sources. The literature search was conducted across multiple databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/), and ScienceDirect (https://www.sciencedirect.com/). The search strategy was developed in collaboration with an experienced medical librarian to ensure comprehensive coverage of the relevant literature. Key words related to neuroendocrine tumours and their treatments were used, including 'neuroendocrine tumours', 'NETs', 'carcinoid', 'pancreatic neuroendocrine tumours', 'treatment', 'therapy', 'surgery', 'chemotherapy', 'targeted therapy' and 'radiotherapy'.

Search strategy. The search strategy was tailored for each database but generally followed a similar structure. Boolean operators (34) were used to combine key words, and filters were applied to limit results to human studies and publications in English. The initial search was conducted in March 2024, and an update was performed in July 2024 to capture any newly published studies.

PubMed database: 'neuroendocrine tumors' OR 'neuroendocrine tumours' OR 'NETs' OR 'carcinoid' OR 'pancreatic neuroendocrine tumor' OR 'gastroenteropancreatic neuroendocrine tumor' AND 'treatment' OR 'therapy' OR 'surgery' OR 'chemotherapy' OR 'targeted therapy' OR 'immunotherapy' OR 'peptide receptor radionuclide therapy' OR 'PRRT'. Filters applied: Humans, English language, Adults (≥18 years), publication date January 2019-July 2024.

Cochrane Library: 'neuroendocrine tumor*' OR 'NET*') in Title/Abstract/Keywords AND 'treatment' OR 'therapy' OR 'chemotherapy' OR 'targeted therapy' OR 'PRRT'.

ScienceDirect: TITLE-ABSTR-KEY 'neuroendocrine tumor*' OR 'NET*' AND ('treatment' OR 'therapy' OR 'immunotherapy' OR 'targeted therapy').

Selection process. Two independent reviewers screened the titles and abstracts of all retrieved studies to assess their eligibility based on the predefined inclusion and exclusion criteria. They then retrieved and reviewed in detail full-text articles of potentially eligible studies. Discrepancies between the reviewers regarding study eligibility were resolved through discussion, and if necessary, a third reviewer was consulted.

Data collection process. Data was extracted using a standardized extraction form explicitly designed for this review. The form captured vital study characteristics, including: i) Study details: Authors, publication year, study design, and sample size. ii) Participant characteristics: Age, sex, tumour type, and tumour grade. iii) Intervention details: Treatment type, duration, and follow-up period. iv) Outcomes: Primary and secondary outcomes as outlined above, including any reported measures of effect and statistical significance.

Data items. The following data items were extracted from each included study, where available: First author and year of publication, study design, sample size, and duration of follow-up. Patient-related variables included median age, sex distribution, tumour site, tumour grade, and disease stage. Treatment-related variables comprised type of therapeutic intervention, treatment regimen, dosing schedule, and duration of therapy. Outcome variables included progression-free survival, overall survival, objective response rate when reported, and treatment-related adverse events. Only outcomes explicitly reported in the original studies were extracted, and no assumptions or imputations were made for missing data.

Risk of bias assessment. The risk of bias for included RCTs was assessed using the Cochrane Risk of Bias Tool (35), which evaluates bias across several domains, including selection, performance, detection, attrition, and reporting. Sensitivity analyses were performed to assess the robustness of the findings by excluding studies with a high risk of bias or those with small sample sizes (36).

Synthesis methods. Due to substantial clinical and methodological heterogeneity across included studies, including differences in tumour sites, study designs, treatment modalities, and reported outcomes, a quantitative meta-analysis was not conducted. Instead, a structured narrative synthesis was performed. Studies were grouped according to treatment modality, and outcomes were summarized descriptively using reported median progression-free survival and overall survival values.

Certainty assessment. The overall certainty of evidence was evaluated qualitatively, taking into account study design, risk of bias, consistency of results, and methodological heterogeneity. Given the inclusion of randomized controlled trials alongside single-arm phase II studies, retrospective analyses, and observational studies, and the substantial heterogeneity in tumour types and treatment strategies, a formal GRADE assessment was not performed. The certainty of evidence was therefore considered moderate to low, depending on treatment modality, with higher confidence attributed to outcomes derived from randomized controlled trials.

Software and statistical analysis. Statistical analyses were conducted using SPSS version 29 (37). All statistical tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference (38). The review results were reported per PRISMA guidelines, ensuring transparency and completeness in reporting (39,40). Key findings were summarized in text and tables, and graphs were used to visually present the results. No formal quantitative meta-analysis was conducted due to marked heterogeneity in study design, tumour types, treatment modalities, and reported outcomes. Statistical analyses were therefore limited to descriptive comparisons and exploratory survival analyses based on reported median progression-free and overall survival values. Descriptive statistics, log-rank tests and χ^2 test were used to summarize reported median progression-free survival and overall survival values across studies. The Φ (phi) effect size was calculated from the χ^2 statistic obtained in the log-rank test, using the standard formula $\Phi=\sqrt{(\chi^2/n)}$, where χ^2 represents the χ^2 value from the survival distribution comparison and n the total number of observations included in the analysis. Exploratory survival analyses were performed using Kaplan-Meier estimates based on extracted median survival times, with censoring applied where appropriate, for illustrative purposes only. Differences in survival distributions between treatment categories were explored using the log-rank test, without adjustment for covariates.

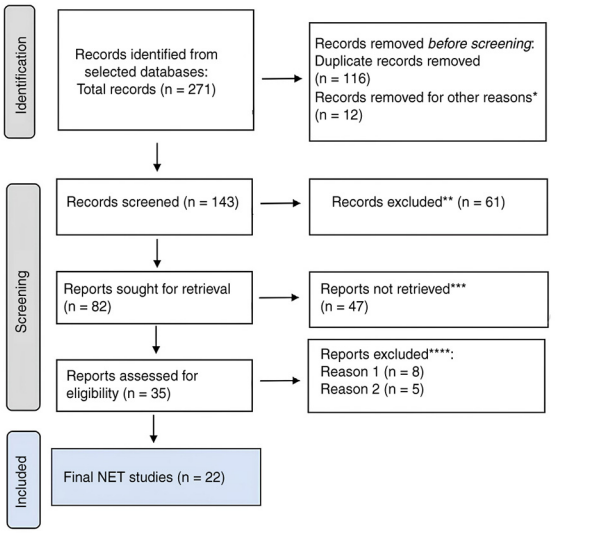

Figure 1. PRISMA framework. Flowchart illustrating the literature search strategy and study selection process according to PRISMA guidelines, including the number of records identified, screened, excluded, and the final number of studies included in the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NET, neuroendocrine tumor.

Results

Study selection and population characteristics. A total of 271 citations were retrieved after scanning the databases mentioned above. After eliminating duplicate entries and excluding 12 items that did not satisfy the search parameters, the list was reduced to 143 remaining articles. Based on the abstracts, 61 studies were excluded from this research as they did not meet the criteria. Additionally, 47 papers were eliminated because they needed the necessary data for extraction and analysis. Another 13 studies were omitted because they were commentary or editorial rather than original research, or they were disregarded, as the full text was not available. Thus, the final analysis was based on a total of 22 search results that met the criteria for this investigation. The search yielded 120 citations for 'neuroendocrine tumours' available on PubMed, three on Cochrane Library, and six on ScienceDirect. The search for 'pancreatic neuroendocrine tumours' led to 8 articles on PubMed, three on Cochrane Library, and one on ScienceDirect.

Table SI (41-62) presents a comprehensive summary of the 22 clinical studies included in this systematic review (Fig. 1), encompassing a diverse range of therapeutic modalities for neuroendocrine tumours and related malignancies. Each study is detailed according to sample size, patient demographics, tumour classification, treatment type and duration, and principal clinical outcomes, including progression-free survival and overall survival.

NETs. Table SI presents a comprehensive overview of the 22 selected studies focused on various treatment approaches for patients with advanced or metastatic NETs and other related solid tumours. Key findings from these studies include each treatment approach's potential benefits and challenges. Therapies, such as nivolumab with ipilimumab and newer agents like belzutifan, are targeted at improving PFS and OS.

A majority of the studies, such as those by Patel *et al* (41), Amaria *et al* (48) and Eggermont *et al* (52), have smaller sample sizes, typically under 100 patients. Only a few studies, like Larkin *et al* (45) and Motzer *et al* (49), have significantly larger sample sizes, reaching nearly 1000 patients. The majority of studies, including Marabelle *et al* (42), Tawbi *et al* (43), and Dummer *et al* (51), report an average patient age centred around the early 60s. Most studies, such as those by Olson *et al* (54) and Taylor *et al* (53), have a male participation rate of 50 to 70%. However, a few studies, like Puca *et al* (44), have a much higher male representation.

Next, we performed a Kaplan-Meier survival analysis (63), for which we prepared Table I. This non-parametric statistical technique is used in survival analysis to estimate the survival function from lifetime data (64,65). Table I includes the key data points necessary to calculate and plot the survival curve. The Status column was used to differentiate between the occurrence of death (coded as 1) and censored data (coded as 0) (66). Censored data represents subjects who did not experience the event during the study period (67). The Kaplan-Meier survival curve (Fig. 2) shows a steady decline in survival probability over up to 60 months. The survival probability begins at 1.0 (or 100%) and gradually decreases, with significant drops occurring at various points, indicating times when multiple events (such as deaths) likely occurred. The curve shows a gradual decline in survival probability over time, indicating that events (such as deaths or failures) occurred consistently throughout the observed period. The curve reflects a steady decrease in survival probability, with survival rates dropping

Table I. Key points from NETs for Kaplan-Meier analysis. Key variables extracted from selected studies for Kaplan-Meier analysis, including survival time (months), event status (death or censored), sex distribution, and treatment category used for stratification.

First author (year)	Time, months	Event status for OS (0=censored; 1=death)	Male, %	Treatment type	Strata	(Refs.)
Patel, 2020	11	1	59	Dual checkpoint inhibitors	Immunotherapy	(41)
Marabelle, 2019	23.5	0	41.2	Pembrolizumab	Immunotherapy	(42)
Puca, 2019	35	1	100	Delta-like protein 3	Targeted therapy	(44)
Larkin, 2019	60	1	66	Dual checkpoint inhibitors	Immunotherapy	(45)
Morizane, 2022	12.5	0	68.8	Etoposide and Cisplatin	Chemotherapy	(47)
Amaria, 2018	15.6	1	75	Neoadjuvant immune checkpoint blockade	Immunotherapy	(48)
Motzer, 2022	55.7	0	73.7	Dual checkpoint inhibitor	Immunotherapy	(49)
Ott, 2020	20.7	1	68	NEO-PV-01 plus nivolumab	Immunotherapy + vaccine	(50)
Eggermont, 2018	9.6	1	56	Pembrolizumab	Immunotherapy	(52)
Olson, 2021	24	1	67	Pembrolizumab plus ipilimumab	Immunotherapy	(54)
Reidy-Lagunes, 2019	24	1	50	Lu-satoreotide tetraxetan	Radiolabelled therapy	(59)
Iyer, 2020	32.7	1	53	Nintedanib	Targeted therapy	(60)

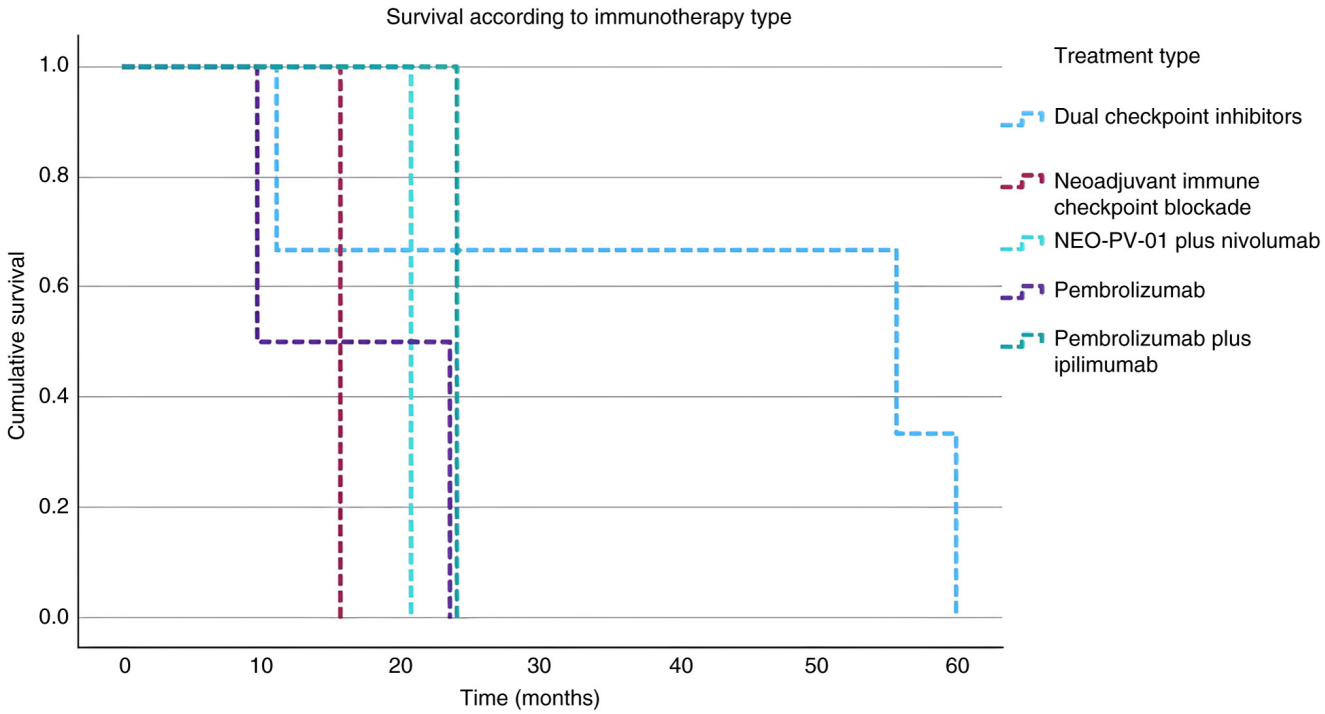

Figure 2. Kaplan-Meier survival curve. Kaplan-Meier survival analysis depicting overall survival over a follow-up period of up to 60 months, stratified by treatment modality. Censored observations are indicated, and survival probabilities are expressed as cumulative proportions over time.

significantly as time progresses, particularly after around 20 to 30 months. Fig. 2 shows the Kaplan-Meier survival curve based on treatment.

Larkin *et al* (45) and Motzer *et al* (49) stand out with the highest OS, both above 55 months. Larkin's study focused on skin melanoma and used nivolumab and ipilimumab. Motzer's study, which focused on advanced renal cell carcinoma, administered a combination of nivolumab and ipilimumab, followed by sunitinib. Eggermont *et al* (52) show the lowest PFS and OS, both under ten months, despite using pembrolizumab for treating small-cell lung cancer. Marabelle *et al* (42) and Olson *et al* (54) have moderate OS (around 20 to 30 months) but relatively low PFS (under five months). Marabelle's study involved pembrolizumab across multiple MSI-H/dMMR tumours, while Olson's focused on skin melanoma with a combination of pembrolizumab and low-dose Ipilimumab.

Morizane *et al* (47) and Patel *et al* (41) show a similar relationship between PFS and OS, with PFS around ten months and OS around 20-25 months. These studies involved Etoposide plus Cisplatin vs. Irinotecan plus Cisplatin in multiple tumour types and ipilimumab plus nivolumab in gastrointestinal and lung NETs, respectively. Iyer *et al* (60) reported an OS of around 35 months, which is notable considering its moderate PFS of about 11 months. This study used nintedanib combined with octreotide LAR for gastrointestinal and pancreatic NETs.

Table II presents the log-rank test for NETs. For chemotherapy, the observed event count is 1, with an expected frequency of 0.27, suggesting that fewer events were anticipated based on the overall survival data. Immunotherapy has an observed count of 7 events, closely matching its expected frequency of 7.03, indicating that the survival outcomes in this group align with expectations. In contrast, the immunotherapy/vaccine group has 0 observed events against an expected frequency of 0.39, suggesting that this treatment group is outperforming expectations, with fewer patients experiencing the event (death). Both radiotherapy and targeted therapy show 1 observed event each, compared to expected frequencies of 0.86 and 1.44, respectively.

The χ^2 test statistic from Table III (χ^2=2.47) falls within the 95% region of acceptance, meaning that there is no statistically significant difference in survival outcomes between the five treatment groups. Any observed differences in survival may be due to random variation rather than the effects of the different treatments. The Φ effect size (Φ=0.80) indicates a moderate relationship between the treatment groups and survival outcomes.

Table IV as well as the scatter plot in Fig. 3 highlights significant variability in PFS and OS outcomes. Treatments involving combinations of Nivolumab and Ipilimumab tend to show higher OS, particularly in studies like Larkin *et al* (45) and Motzer *et al* (49). In contrast, Pembrolizumab alone or in combination, shows more varied outcomes depending on the tumour type and setting. The plot also reveals a pattern where specific treatments provide long-term survival benefits even if they don't immediately prolong PFS, as seen in studies like Olson *et al* (54) and Iyer *et al* (60).

The middle blue dashed line at HR=1 indicates no effect, serving as a reference point. Most studies have hazard ratios that hover around the null value of 1, indicating that the treatments under consideration have varying degrees of effectiveness on PFS and OS. Studies like Tawbi *et al* (43), Morizane *et al* (47), and Rinke *et al* (61) show hazard ratios greater than 1, which could suggest a potential reduction in survival compared to the baseline or control. Conversely, other studies like Puca *et al* (44) and Reidy-Lagunes *et al* (59) have HRs below 1, indicating a possible survival benefit.

Risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool was performed only for randomized controlled trials, in accordance with Cochrane recommendations. Observational studies, retrospective analyses, single-arm phase I/II trials, and basket trials without randomization were not suitable for RoB 2 assessment and were therefore excluded from this analysis. Of the 22 included studies, five met the criteria for randomized controlled trials and were assessed for risk of bias (Tables V and VI). Two trials [Larkin *et al* (45) and Motzer *et al* (49)] were judged to have a low overall risk of bias, with low risk across most bias domains. The remaining three studies [Tawbi *et al* (43), Morizane *et al* (47) and Singh *et al* (62)] presented some concerns regarding overall risk of bias, mainly related to deviations from intended interventions or open-label study designs. No trial was classified as having a high overall risk of bias.

Table II. Log-rank test for NETs. Observed and expected event frequencies for each treatment category, used to assess differences in survival distributions across groups using the log-rank test.

Group	Observed frequency	Expected frequencies
Chemotherapy	1	0.274242424
Immunotherapy	7	7.033982684
Immunotherapy/vaccine	0	0.385353535
Radiotherapy	1	0.861544012
Targeted therapy	1	1.444877345

Table III. χ^2 test for comparing the survival distributions. χ^2 statistics, degrees of freedom, and effect size (Φ coefficient) summarizing the comparison of survival distributions among the different treatment modalities.

Statistic	Value	Description
Number of groups (k)	5	Number of groups
Sample size (n)	10	Sample size
χ^2 value	2.465397	χ^2 test statistic
m	0	Estimated parameters
DF	4	DF=k-m-1=5-0-1=4
Φ effect size	0.796528	$\Phi=\sqrt{(\chi^2 / n)}$

DF, degrees of freedom.

Table IV. Median PFS and OS according to treatment type. Median PFS and OS values reported across studies, stratified by treatment modality, illustrating variability in survival outcomes among different therapeutic approaches.

First author (year)	Median PFS, months	Median OS, months	Strata/treatment type	(Refs.)
Patel, 2020	4.1	11	Dual checkpoint inhibitors (immunotherapy)	(41)
Marabelle, 2019	2	23.5	Pembrolizumab (immunotherapy)	(42)
Puca, 2019	5.5	35	Delta-like protein 3 (targeted therapy)	(44)
Larkin, 2019	11	60	Dual checkpoint inhibitors (immunotherapy)	(45)
Morizane, 2022	5.6	12.5	Etoposide + Cisplatin (chemotherapy)	(47)
Amaria, 2018	6.7	15.6	Neoadjuvant ICB (immunotherapy)	(48)
Motzer, 2022	11.2	55.7	Dual checkpoint inhibitor (immunotherapy)	(49)
Ott, 2020	7.2	20.7	NEO-PV-01 + Nivolumab (immunotherapy + vaccine)	(50)
Eggermont, 2018)	5.5	9.6	Pembrolizumab (immunotherapy)	(52)
Olson, 2021	9.2	24	Pembrolizumab + Ipilimumab (immunotherapy)	(54)
Reidy-Lagunes, 2019	9.8	24	Lu-satoreotide tetraxetan (radiolabelled therapy)	(59)
Iyer, 2020	12.1	32.7	Nintedanib (targeted therapy)	(60)

Table V. Study design of included clinical studies. Distribution of the included studies according to study design, including randomized controlled trials, single-arm phase II trials, retrospective cohort studies, observational studies, and exploratory basket trials.

Study type	Number of studies
Randomized controlled trials	5
Single-arm phase II trials	9
Retrospective cohort studies	4
Observational prospective studies	3
Basket/exploratory trials	1

Discussion

This systematic review provides an integrated evaluation of therapeutic strategies across neuroendocrine tumours and selected related malignancies, highlighting the diversity of available treatments and their variable impact on survival outcomes.

Across the included studies, immunotherapy emerged as a central area of investigation. Dual checkpoint blockade with nivolumab plus ipilimumab demonstrated durable benefits in several cohorts, with overall survival exceeding 55 months in certain populations, as shown by Larkin *et al* (45) and Motzer *et al* (49). These results confirm the potential of immune-based regimens to extend long-term survival, even though toxicity profiles and treatment costs remain limiting factors (68,69). This finding is also stated by Pánczél *et al* (70) who concluded that dual checkpoint blockade with ipilimumab and nivolumab achieved higher response and disease control rates, albeit with increased toxicity, suggesting a potential benefit for selected patients. In contrast, pembrolizumab monotherapy and combination regimens yielded more heterogeneous outcomes. For example, Eggermont *et al* (52) reported OS under 10 months in small-cell lung cancer, whereas Marabelle *et al* (42) observed more favourable responses in mismatch repair-deficient tumours. Similar to this, Hektoen *et al* (71) noticed a doubling in patients surviving more than 2 years when comparing improvement in survival with pembrolizumab relative to previous platinum-based chemotherapy. It continues to be used in the management of high-grade or poorly differentiated NETs and related carcinomas. The trial by Morizane *et al* (47) compared etoposide-cisplatin with irinotecan-cisplatin in advanced digestive neuroendocrine carcinoma, showing no significant difference in survival but confirming both regimens as standard first-line options. Choucair *et al* (72) investigated Irinotecan in combination with cisplatin for treating advanced poorly differentiated GEP-NETs, and in phase II of his trial, the researchers found that the objective response rate was comparable between IP and EP in small-cell NETs.

Targeted therapies also demonstrated clinically relevant benefits. Nintedanib in non-pancreatic gastroenteropancreatic NETs was associated with PFS of 11 months and OS approaching 33 months. Similarly, rovalpituzumab tesirine, directed at DLL3 in neuroendocrine prostate cancer, showed promising efficacy.

Another notable therapeutic avenue is radiolabelled peptide receptor therapy and other radiolabelled approaches. The trial by Reidy-Lagunes *et al* (59) demonstrated that Lu-satoreotide tetraxetan achieved a median PFS of 21 months and favourable long-term OS rates in somatostatin receptor-positive NETs. This is similar to what Wild *et al* (73) found. In their phase I/II study, Lu-satoreotide tetraxetan, administered at a median cumulative activity of 13.0 GBq over three cycles, has an acceptable safety profile with a promising clinical response in patients with progressive, SSTR-positive NETs.

From a clinical practice perspective, the findings summarized support an individualized approach to neuroendocrine tumour management. Peptide receptor radionuclide therapy demonstrated the most durable disease control, with

Table VI. Overall risk of bias. Evaluation of risk of bias across five domains: Randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting, for the five randomized controlled trials included in the review, together with the overall risk of bias judgment for each study.

First author (year)	Bias arising from the randomization process (Selection bias)	Bias due to deviations from intended interventions (Performance bias)	Bias due to missinge outcom data (Attrition bias)	Bias in measurement of the outcome (Detection bias)	Bias in selection of the reported (Reporting result bias)	Overall risk of bias	(Refs.)
Larkin, 2019	Low risk	Some concerns	Low risk	Low risk	Low risk	Low risk	(45)
Motzer, 2022	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk	(49)
Tawbi, 2022	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	(43)
Morizane, 2022	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	(47)
Singh, 2024	Low risk	High risk (open-label design)	Some concerns	Low risk	Low risk	Some concerns	(62)

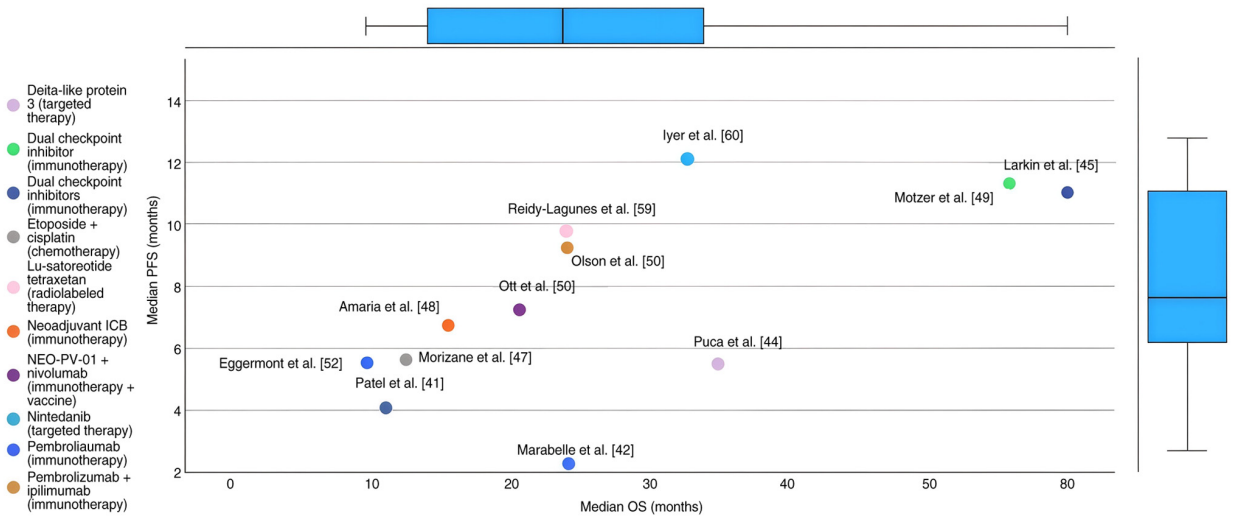

Figure 3. Hazard ratios for PFS and OS. Forest plot showing hazard ratios for progression-free survival and overall survival across selected studies. The vertical reference line at HR=1 indicates no treatment effect, with values below 1 suggesting a survival benefit and values above 1 indicating reduced survival.

^{177}Lu-DOTATATE and Lu-satoreotide tetraxetan achieving the longest PFS in somatostatin receptor-positive tumours (59,62). In addition, dual immune checkpoint blockade with nivolumab and ipilimumab was associated with the longest OS in their selected cohorts (45,49). From a policy and future research perspective, the heterogeneity of outcomes highlights the need for equitable access to advanced therapies such as PRRT and combination immunotherapy (59,62). Healthcare policies should facilitate referral to specialized centres and support reimbursement for these treatments. Future research should prioritize NET-specific randomized trials and biomarker-driven approaches, building on existing evidence for PRRT and immunotherapy (45,49,62), to optimize patient selection, treatment sequencing, and long-term outcomes.

Despite encouraging results, the variability of outcomes across treatment modalities reflects the challenges of managing NETs. Some regimens, such as checkpoint inhibitors, may provide long-lasting benefit in a subset of patients but limited responses in others. Moreover, the included studies varied substantially in sample size, design, and endpoints. Thus, the analysis indicates that immunotherapy, targeted agents, and radiolabelled therapies offer meaningful clinical benefits for selected patients with NETs outside the pancreas.

The overall certainty of evidence for the main outcomes was considered moderate for PFS and OS in treatment modalities supported by randomized controlled trials, particularly for dual immune checkpoint inhibition and peptide receptor radionuclide therapy. In contrast, the certainty of evidence was

low for outcomes derived primarily from single-arm phase II studies, retrospective analyses, and exploratory trials, due to limited sample sizes, lack of randomization, and heterogeneity in tumour types and treatment regimens.

This study presents some limitations. First of all, it includes a mix of RCTs, single-arm studies, and retrospective analyses. This variability in study design introduces heterogeneity that can affect the comparability of outcomes across studies. Including studies with different methodologies, sample sizes, and bias levels may have influenced the overall results. We included in the analysis various cancer types, stages, and patient demographics. While providing a broad overview of treatment effects, this diversity also limits the ability to draw specific conclusions about individual treatments' efficacy for particular cancer subtypes. Differences in tumour biology, patient characteristics, and previous treatments contribute to the variability in survival outcomes. We also found many small sample sizes and single-arm study designs, limiting the robustness and generalizability of the results.

To sum up, immunotherapy, particularly dual checkpoint blockade with nivolumab and ipilimumab, demonstrated the most durable effects, with progression-free survival around 11 months and overall survival extending to 55-60 months in advanced settings. Single-agent checkpoint inhibitors showed variable results: pembrolizumab achieved PFS between 2 and 5 months, with OS ranging from 9.6 months in small-cell lung cancer to 23.5 months in mismatch repair-deficient tumours. Chemotherapy remained a mainstay for high-grade carcinomas, with etoposide-cisplatin or irinotecan-cisplatin achieving OS of approximately 11-12.5 months. Targeted therapies, such as nintedanib, improved survival outcomes (PFS 11 months; OS 32.7 months), indicating benefit in selected cases. Radiolabelled therapies like Lu-satoreotide tetraxetan further extended PFS to 21 months, with long-term survival rates of 85% at two years and 63% at three years. Collectively, results emphasize tailored, multimodal strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ADC, SD, MC, LM, LSNC, ACIP, RAN, CAC and NC contributed to the conceptualization and design of the study. ADC and SD developed the methodology. MC and LM performed the formal analysis. LSNC and ACIP were responsible for data curation. RAN and CAC conducted the investigation and managed resources. NC performed the statistical analysis and data validation. ADC drafted the original manuscript. SD, MC and LM critically revised and edited the manuscript. CAC generated figures and tables. NC supervised the project. ADC and SD acquired funding. SD and ADC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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