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Recognition and Management of Adverse Reactions to Immunotherapy in Gynecologic Oncology: A Comprehensive Review

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Abstract: *Background:* Immune checkpoint inhibitors (ICIs) have transformed gynecologic cancer treatment, but their use is complicated by immune-related adverse events (irAEs) that pose significant clinical challenges. *Objective:* This review systematically summarizes the epidemiology, mechanisms, recognition, and management of irAEs in gynecologic malignancies, highlighting controversies and future directions. *Main content:* IrAEs occur in a substantial proportion of gynecologic oncology patients, with varying onset and severity profiles by ICI class and cancer type. Pathophysiological mechanisms include off-target T-cell activation and molecular mimicry. Recognition requires vigilance toward multi-organ toxicities. Management follows CTCAE-guided tiered strategies: mild events permit continued immunotherapy with supportive care, while severe toxicities require treatment interruption and corticosteroids, with escalation to second-line agents in refractory cases. Special considerations include combination regimens, elderly patients, and immunotherapy rechallenge decisions. *Conclusion:* Optimal irAE management requires multidisciplinary collaboration, individualized risk assessment, and standardized protocols. Future research should focus on predictive biomarkers and preventive strategies to maximize efficacy while ensuring safety.

Keywords: Gynecologic cancers; Immune checkpoint inhibitors; Immune-related adverse events (irAEs); Toxicity management

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1. Introduction and positioning of research value

1.1. Current status of immunotherapy for gynecologic cancers

The integration of immune-checkpoint inhibitors (ICIs) into gynecologic oncology represents a transformative

therapeutic advance. These agents are rapidly moving from late-line to first-line treatment, driven by pivotal trials showing that adding pembrolizumab to chemotherapy significantly prolongs survival in advanced cervical and endometrial cancers. Current research focuses on bispecific antibodies and rational combinations with anti-angiogenics or PARP inhibitors to reprogram the immunosuppressive tumor microenvironment. However, inter-patient response heterogeneity remains the central challenge. Future progress depends on refining actionable biomarkers (PD-L1, MSI-H/dMMR, and emerging signatures) and developing strategies to convert "cold" tumors into ICI-sensitive phenotypes, thereby advancing precision-based care in gynecologic immuno-oncology [1].

2.2. Clinical significance of the distinctive toxicity spectrum of immune checkpoint inhibitors

While immune-checkpoint inhibitors (ICIs) exert antitumor activity through systemic immune activation, they inevitably provoke immune-related adverse events (irAEs)—the central dilemma limiting their clinical use. irAEs exhibit a broad and complex clinical spectrum, involving not only commonly affected organs such as the skin, gastrointestinal tract, liver/biliary system, and endocrine glands, but also toxicities unique to the female reproductive system. Their toxicity profile further differs according to the target pathway (e.g., CTLA-4 vs PD-1/PD-L1 blockade). The underlying mechanisms are multifaceted, likely encompassing excessive T-cell activation, autoantibody generation, and direct immune assault on healthy tissue. Beyond causing substantial morbidity and healthcare burden, irAEs can compel dose reduction or treatment discontinuation, thereby compromising long-term therapeutic efficacy [2].

2.3. The pivotal impact of adverse-event management on therapeutic benefit

As ICIs have become a mainstay of treatment for multiple cancers, the management of irAEs has emerged as an integral part of oncologic care. Accumulating evidence indicates that the occurrence of irAEs is associated with therapeutic efficacy, yet severe irAEs can pose formidable clinical challenges and compromise patient outcomes. In gynecologic malignancies, timely recognition and intervention for irAEs are essential to preserve treatment continuity. The principal clinical hurdles at present include difficulties in toxicity prediction, an incomplete understanding of organ-specific reaction mechanisms, and the delicate risk–benefit balance in special scenarios such as hormone-replacement therapy. Establishing standardized, multidisciplinary management strategies will help maximize the clinical benefits of immunotherapy while safeguarding patient safety [3].

3. Epidemiological characteristics of adverse reactions to immunotherapy for gynecological tumors

3.1. Overall incidence rate and temporal distribution pattern

The use of immune-checkpoint inhibitors in gynecologic oncology is expanding rapidly, and immune-related adverse events (irAEs) have become a major clinical concern. Published data indicate that the overall incidence of irAEs in patients with gynecologic malignancies is approximately 30–60 %. These toxicities display a characteristic time-to-onset profile: most appear within 2–12 weeks of treatment initiation, but delayed reactions can emerge months—or even years—after therapy has been discontinued. Notably, the median onset differs markedly among organ systems: dermatologic events are usually the earliest (median 3–6 weeks), whereas endocrine toxicities such as thyroid dysfunction typically manifest at 8–12 weeks. Grade 3–4 events occur in roughly 10–15 % of patients, and permanent discontinuation of checkpoint blockade is required in 3–5 % [4].

3.2. Specific adverse reaction spectrum of gynecological tumors

Patients with gynecologic cancers exhibit a unique spectrum of immune-related adverse events (irAEs). In cervical cancer, common pembrolizumab-associated adverse events include fatigue (9.2%), diarrhea (8.2%), and hypothyroidism (10.2%). Endometrial cancer patients are more prone to endocrine toxicities (particularly thyroid dysfunction) and arthralgia. Ovarian cancer patients demonstrate higher incidences of gastrointestinal toxicities and cutaneous reactions. Notably, gynecologic organ-specific toxicities include vaginitis (8–12%), pelvic inflammatory reactions (5–8%), and premature ovarian failure (3–5%) [5]. Compared to other cancer types, gynecologic cancer patients have a significantly elevated risk of musculoskeletal toxicities.

3.3. Differences in toxicity among different immune checkpoint inhibitors

Distinct toxicity profiles are observed among different classes of immune checkpoint inhibitors. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (e.g., ipilimumab) exhibit a significantly higher overall incidence of immune-related adverse events (irAEs) (60%–85%) compared to programmed cell death protein 1/programmed death-lig1 (PD-1/PD-L1) inhibitors (15%–30%). In gynecologic cancers, CTLA-4 inhibitors are more frequently associated with colitis (17% vs. 5%) and hypophysitis (6% vs. 1%). PD-1 inhibitors more commonly cause thyroid dysfunction (15% vs. 3%) and pneumonitis (5% vs. 1%). Combination therapy (e.g., CTLA-4 + PD-1 inhibitors) results in additive toxicities, with grade 3–4 adverse events occurring in 55%–60% of patients. Furthermore, the PD-L1 inhibitor atezolizumab demonstrates a relatively lower risk of cutaneous toxicity (10% vs. 25%) but a higher risk of thrombocytopenia (8% vs. 3%) in patients with ovarian cancer [6]. These variations underscore the necessity of developing individualized monitoring strategies tailored to specific treatment regimens.

4. Pathophysiological mechanisms of immune-related adverse events

4.1. Mechanisms of off-target effects of immune checkpoint inhibitors

Immune checkpoint inhibitors unleash T cells from their physiologic brakes, yielding potent anti-tumor activity, yet the same systemic immune re-awakening can turn against healthy organs. Two non-mutually exclusive pathways drive these collateral injuries: first, the antibody itself may bind innocent tissues and ignite complement- or Fc-mediated assault; second, unleashed T cells expand and recruit additional arms of immunity, amplifying a self-sustaining inflammatory loop. Clinically, CTLA-4 blockade exacts a heavier toll than PD-1/PD-L1 interception, underscoring target-specific risk profiles. Intriguingly, pre-clinical work reveals that aged tumor-bearing mice, but not their young counterparts, succumb to multi-organ failure under PD-1 blockade, hinting that senescent immune landscapes tilt the balance toward toxicity [7].

4.2. Gynecological tissue-specific autoimmune response

Immunotherapy for gynecologic cancers may trigger unique reproductive system toxicities, often attributed to molecular mimicry where tumor antigens resemble self-antigens in healthy tissues. For example, cervical cancer patients treated with pembrolizumab have developed organ-specific toxicities such as vaginitis and cervicitis, hypothesized to arise from cross-reactive immune responses. HPV-activated immune cells may erroneously attack normal cervical epithelium sharing structural similarities with tumor antigens. Additionally, cancer-testis antigens—frequently overexpressed in ovarian cancers and physiologically present in immune-privileged sites like ovaries—can become targets of off-target immune attack when engaged by immunotherapy, potentially causing

ovarian dysfunction [8].

5. Systematic identification of common adverse reactions

5.1. Clinical manifestations and grading of skin toxicity

Cutaneous toxicities are among the most frequently reported adverse events in immunotherapy for gynecologic cancers, with diverse clinical manifestations including rash (15%), pruritus (16%), and skin pigmentation changes. According to the Common Terminology Criteria for Adverse Events (CTCAE), these toxicities are commonly graded as mild to moderate (grade 1–2, 36.4%), though severe reactions (grade 3, 5.1%; grade 4, 5.1%) may also occur. Typical presentations encompass maculopapular rash, lichenoid dermatitis, and vitiligo-like depigmentation, which generally emerge within 2 to 8 weeks after treatment initiation. Notably, the development of cutaneous toxicity may carry prognostic significance, as its occurrence has been associated with improved treatment response [9].

5.2. Recognition of gastrointestinal tumors

Gastrointestinal toxicities are among the most frequently reported adverse events associated with immunotherapy for gynecological cancers. The most common manifestations include elevated transaminases (occurring in approximately 36.4% of patients), nausea, diarrhea, and constipation. These events are typically graded by severity: Grade 1-2 toxicities encompass mild diarrhea or asymptomatic elevations in liver enzymes, while Grade 3 events (reported in about 2.6% of cases) may present as severe colitis or significant hepatic dysfunction. The onset of these toxicities displays considerable temporal heterogeneity and can occur at any point during the treatment course; however, they most commonly emerge between 6 and 14 weeks after initiation of therapy [1]. It is particularly important to note that although pancreatitis—often signaled by elevated lipase levels—is less common, its prompt recognition and management are critical [10].

5.3. Monitoring for endocrine system abnormalities

Endocrine toxicities represent a clinically significant concern in the immunotherapy of gynecological cancers. The most common manifestation is thyroid dysfunction, encompassing both thyrotoxicosis and hypothyroidism. These abnormalities frequently arise within 4 to 12 weeks following treatment initiation, with a reported incidence of up to 36.4%. Adrenal insufficiency, while less common, is a potentially serious toxicity that necessitates prompt hormone replacement therapy. Essential monitoring should include regular assessment of thyroid function (TSH and FT4) and morning cortisol levels. Clinicians should maintain a high index of suspicion for non-specific symptoms such as persistent fatigue and unexplained weight changes, which may signal endocrine dysfunction [4].

5.4. Gynecologic organ–specific toxic manifestations

Immunotherapy for gynecological cancers can induce distinct organ-specific toxicities affecting the female reproductive tract. These adverse events include long-term vaginal changes (28.2%), dyspareunia (15.3%), and vulvovaginitis. Clinical manifestations may involve local fibrosis, skin hyperpigmentation (12.8%), or a chronic inflammatory state. Unlike toxicities associated with conventional chemotherapy, immunotherapy-related gynecologic adverse events often exhibit a delayed onset, potentially emerging several months after treatment cessation [11]. Pelvic inflammatory reaction represents another unique presentation, which can mimic disease progression on imaging and requires differentiation through radiological assessment and biopsy for accurate diagnosis.

6. Evidence-based tiered management strategy

6.1. Interpretation of international guideline consensus

Current international guidelines consistently integrate the management of immune checkpoint inhibitor-related adverse events (irAEs) as a key component of immunotherapy for gynecological cancers. Guidelines advocate a stepwise management strategy guided by adverse event severity (CTCAE grading), alongside organ-specific interventions. For patients with gynecological malignancies, particular attention is given to endocrine toxicities, such as thyroid dysfunction, and the management of reproductive system-specific irAEs. A multidisciplinary collaborative approach is recommended for complex cases, especially in scenarios involving hormone replacement therapy or other specialized considerations [12].

6.2. Management protocol for grade 1–2 adverse reactions

For mild (Grade 1) adverse events, guideline recommendations typically support continuing immunotherapy with close monitoring alongside symptomatic management [13]. Cutaneous toxicities, such as rash (reported incidence 4.2-21.7%), are commonly managed with topical corticosteroids and antihistamines [14]. Management of Grade 2 toxicities generally requires postponing immunotherapy and initiating oral corticosteroids (e.g., prednisone at 0.5-1 mg/kg/day or equivalent) until symptoms improve to Grade ≤ 1 [14]. Particular vigilance for thyroid dysfunction is advised in patients with gynecological cancers, given its reported incidence of 6.3-17.4%. Gastrointestinal toxicities, such as diarrhea, are managed with antidiarrheal agents, with endoscopic evaluation considered in select cases.

6.3. Management protocol for grade 3–4 adverse reactions

Severe (Grade 3-4) irAEs necessitate the immediate discontinuation of immunotherapy and inpatient management, typically initiated with high-dose corticosteroid pulse therapy (e.g., methylprednisolone 1–2 mg/kg/day) [4]. For steroid-refractory cases, guideline consensus suggests considering second-line immunosuppressive agents, such as the IL-6 receptor antagonist tocilizumab or the TNF-α inhibitor infliximab [15]. Evidence indicates that the occurrence of Grade 3-4 irAEs may be associated with poorer overall survival (HR=1.41), underscoring the need to carefully balance the necessity of continued immunotherapy [16]. Particular attention is required for potentially life-threatening toxicities such as immune-mediated pneumonitis (incidence 4.2-6.3%), as these patients may require prolonged immunosuppression and respiratory support.

6.4. Principles for the rational use of glucocorticoids

Corticosteroids serve as the cornerstone for managing irAEs, with an emphasis on dose individualization and treatment duration optimization [4]. Initial therapy should employ a sufficient dose (e.g., ≥ 0.5 mg/kg/day prednisone equivalent), followed by a slow taper over 4-8 weeks upon symptom control [15]. Long-term use necessitates vigilant monitoring for adverse effects including infection risk, osteoporosis, and hyperglycemia. Notably, corticosteroids may potentially attenuate the antitumor efficacy of immunotherapy, requiring a careful balance between toxicity management and preservation of treatment benefit. For patients with gynecological cancers, special attention should be paid to the potential impact of corticosteroids on the hypothalamic-pituitary-gonadal axis and the consequent hormone replacement needs [17].

7. Management challenges in special clinical situations

7.1. Overlapping toxicities of combination regimens

Immune checkpoint inhibitor (ICI) combination regimens demonstrate significant synergistic antitumor effects in gynecological cancers, yet introduce distinct toxicity management challenges. Clinical data reveal that the incidence of immune-related adverse events (irAEs) is markedly higher with combination therapy than with monotherapy. For instance, regimens combining anti-CTLA-4 and anti-PD-1/PD-L1 agents can report irAE rates as high as 76.5% [18]. This synergistic toxicity is attributed to the concurrent stimulation of complementary T-cell activation pathways, which amplifies systemic inflammatory responses and exacerbates off-target effects. In the context of gynecological malignancies, immunochemotherapy combinations are associated with an all-grade adverse event rate of 86.8% and a grade ≥ 3 event rate of 35.9%, both significantly exceeding rates observed with monotherapy. Notably, combination therapies may alter the reliability of traditional tumor biomarkers, necessitating heightened clinical vigilance to discern potential irAE interference during efficacy assessment [19].

7.2. Risk management in older adults

Elderly patients with gynecological malignancies exhibit distinct risk profiles when undergoing immunotherapy [4]. This heightened risk is closely linked to age-related immunosenescence, diminished organ functional reserve, and complex polypharmacy [20]. Clinical observations have indicated increased toxicity in specific vulnerable subgroups. For instance, among elderly patients with baseline renal impairment, the incidence of treatment-related serious adverse events and immune-related adverse events (irAEs) reached 11.5% and 12.8%, respectively, rates notably higher than those in the broader population. Subgroup analysis further revealed that elderly patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 experienced a severe adverse event rate as high as 14.8%, underscoring the critical importance of comprehensive baseline assessment, including functional status. Furthermore, the management of irAEs in this population requires a highly individualized approach due to altered corticosteroid metabolism and increased susceptibility to infections associated with prolonged immunosuppressive use [21].

7.3. Late-onset toxicity surveillance in long-term survivors

As the number of long-term survivors of gynecologic cancers treated with immunotherapy increases, the surveillance of late-onset toxicities has emerged as a significant clinical challenge. Available data indicate that immune-related adverse events (irAEs) can persist or even develop after a median follow-up of 12.6 months, with certain endocrine toxicities, such as thyroid dysfunction, potentially resulting in permanent damage. Among long-term survivors of cervical cancer, late-onset adverse events associated with pembrolizumab include persistent arthralgia and endocrine dysfunction. Of particular concern is the evidence that immunotherapy may exert long-lasting immunomodulatory effects, possibly through alterations in T-cell metabolism and gut microbiome composition. These findings necessitate continuous, long-term surveillance of survivors' endocrine, cardiovascular, and rheumatologic health. Currently, the mechanisms and predictive biomarkers for these late toxicities remain poorly defined, highlighting the urgent need to establish dedicated long-term follow-up registries to accumulate robust evidence [22].

8. Current controversies and unresolved issues

8.1. The clinical translation dilemma of biomarker prediction

Despite numerous research efforts aimed at identifying biomarkers predictive of immunotherapy toxicity,

significant translational challenges remain within the field of gynecologic oncology. Existing evidence suggests that features such as tumor-infiltrating lymphocytes and specific genomic alterations may hold predictive value; however, the clinical application of these markers still lacks standardized validation. Notably, in a study of 49 patients with gynecologic malignancies, the absence of transcriptomic signatures was identified, making immune-related toxicity the sole clinical predictor of response to immune checkpoint inhibitor therapy ($p = 0.008$) [23]. While the detection of peripheral blood immune signatures has shown potential for identifying severe irAEs, their sensitivity and specificity require confirmation through large-scale clinical trials. Concurrently, the influence of factors such as metabolic reprogramming and the gut microbiome on treatment response is under active investigation, potentially offering novel directions for future biomarker development.

8.2. Benefit-risk profile of hormone replacement therapy

Endocrine toxicity induced by immunotherapy, particularly hypothyroidism and hypophysitis, often necessitates long-term hormone replacement therapy. However, existing data indicate that the optimal dosing regimen for thyroid hormone replacement remains unclear, leading to significant variations in clinical practice [24]. The situation is further complicated by the fact that hormone replacement therapy is not a universal solution. While it can counteract age-related hormonal decline, it may also trigger various adverse events [25]. This balance is especially delicate in patients with gynecological cancers, where the hormonal milieu can simultaneously influence both tumor progression and the efficacy of immunotherapy. Currently, there is a lack of studies on hormone replacement regimens specifically designed for immunotherapy-related endocrine toxicity, particularly for the subset of patients with estrogen- and progesterone-sensitive gynecological tumors.

8.3. Decision-making criteria for rechallenge with immunotherapy

The clinical decision of whether to restart immunotherapy following the occurrence of severe immune-related adverse events (irAEs) poses a significant challenge due to considerable uncertainty. Available observational studies indicate that up to 76.2% of patients may develop multiple irAEs, which can include persistent symptoms like arthralgia. Although the development of severe irAEs is associated with overall survival, the direction of this causality remains unclear. This uncertainty is particularly pronounced in gynecologic oncology, where safety data for rechallenging patients after organ-specific toxicities—such as oophoritis or cervicitis—are notably lacking. Clinicians must carefully weigh the risk of disease progression against the possibility of inducing recurrent, and potentially more severe, irAEs. Currently, this complex decision-making process lacks support from established risk-stratification tools or validated predictive models [14].

9. Prospective research directions and technical approaches

9.1. Construction and validation of predictive models for toxicity

There is an urgent clinical need to establish reliable predictive models for immune-related adverse events (irAEs). Such models are crucial for identifying high-risk patient populations and enabling more precise assessment of the clinical risk-benefit ratio associated with immunotherapy. Recent studies highlight this need in gynecologic cancers, where, in the absence of informative transcriptomic signatures, the occurrence of immune-related toxicity emerged as the only statistically significant predictor of response to immune checkpoint inhibitor therapy. Meanwhile, machine learning-based integrative analytical approaches have demonstrated considerable potential. For instance, an immune-related risk model developed in ovarian cancer research not only predicts patient

prognosis but also offers insights for developing novel therapeutic strategies. Future research should focus on constructing a multidimensional predictive framework that incorporates genomic features (e.g., PD-L1 expression levels), tumor microenvironment characteristics (e.g., tumor-infiltrating lymphocytes), and clinical parameters [26].

9.2. Randomized clinical trials of prophylactic intervention strategies

With the increasing use of immune checkpoint inhibitors (ICIs) in gynecologic cancers such as recurrent/metastatic cervical cancer, the conduct of clinical trials investigating prophylactic interventions has become critically important. Emerging evidence suggests that eosinophilia may serve a dual role—acting both as a predictive biomarker for clinical benefit from ICIs and as a potential precursor to organ dysfunction. This dual function provides a promising entry point for targeted prevention strategies. Future research should systematically evaluate the benefit-risk profile of prophylactic immunomodulators (e.g., low-dose corticosteroids) in specific high-risk patient subsets. Concurrently, there is a need to explore biomarker-guided, stratified intervention approaches. Moreover, for the endocrine and reproductive system toxicities unique to gynecologic malignancies, dedicated prophylactic intervention protocols must be designed [27].

10. Synthesis and principal clinical recommendations

10.1. Multidisciplinary team-based management approach

The management of immune-related adverse events (irAEs) in gynecologic oncology necessitates a well-coordinated multidisciplinary team (MDT) model. This model integrates expertise from diverse specialties, including oncology, dermatology, gastroenterology, endocrinology, and rheumatology [14]. Such a collaborative approach is essential for providing precise diagnosis and management tailored to toxicities affecting different organ systems. It proves particularly critical in complex cases, such as those involving corticosteroid-refractory adverse events or patients with pre-existing autoimmune conditions. The MDT should establish standardized consultation protocols and communication mechanisms to ensure the timely recognition and intervention of rare toxicities, for instance, immune-mediated ototoxicity. Clinical experience underscores the unique value of rheumatologists in managing rheumatic irAEs, where their expertise is crucial for balancing the need for immunosuppressive therapy with the preservation of antitumor efficacy [28].

10.2. Individualized evaluation of benefit-risk profile

Treatment with immune checkpoint inhibitors (ICIs) in gynecologic cancers mandates an individualized risk-benefit assessment for each patient. Key elements of this assessment include tumor type and stage, PD-L1 expression status, prior treatment history, pre-existing conditions (particularly autoimmune diseases), and patient age. Special attention to toxicity risk is required for elderly patients and those with multiple comorbidities, which may necessitate treatment regimen adjustments or intensified monitoring. It is noteworthy that while the occurrence of irAEs may be associated with treatment response, severe (grade 3-4) toxicities can adversely affect patient prognosis. This underscores the need for dynamic clinical decision-making, continuously weighing the benefits of continuing therapy against the risks. For patients with recurrent or metastatic cervical cancer, therapy should not be summarily discontinued upon the development of irAEs. Instead, management should be precisely tailored based on both the severity of the toxicity and the observed antitumor response [29].

10.3. Key points for standardization of treatment

The standardized management of immunotherapy in gynecologic cancers should adhere to the following core principles. First, institutional standardized diagnostic and treatment pathways must be established, strictly referencing international consensus guidelines such as the NCCN Guidelines for Management of Immunotherapy-Related Toxicities Second, a stepwise intervention strategy based on toxicity grading must be implemented: for Grade 1-2 toxicities, consider continuing immunotherapy with supportive care; Grade 3 toxicities typically require treatment interruption and initiation of corticosteroid therapy; Grade 4 toxicities usually necessitate permanent discontinuation and intensified immunosuppressive treatment. Particular emphasis must be placed on standardizing corticosteroid use, including dosage selection (e.g., prednisone at 1-2 mg/kg/day equivalent), tapering strategies (a gradual taper over at least 4-6 weeks), and the choice of second-line immunosuppressants for refractory cases. For irAEs with potential long-term sequelae, such as endocrine toxicities, ongoing monitoring mechanisms are essential—for example, recognizing the potential need for lifelong hormone replacement in patients with thyroid dysfunction. Finally, enhancing patient education, establishing symptom alert systems, and ensuring rapid-access clinical pathways are critical to guarantee the early identification and intervention of adverse events [30].

Disclosure statement

The authors declare no conflict of interest.

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