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REVIEW

Adenosine triphosphate induced cell death: Mechanisms and implications in cancer biology and therapy

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Abstract

Adenosine triphosphate (ATP) induced cell death (AICD) is a critical cellular process that has garnered substantial scientific interest for its profound relevance to cancer biology and to therapeutic interventions. This comprehensive review unveils the intricate web of AICD mechanisms and their intricate connections with cancer biology. This review offers a comprehensive framework for comprehending the multifaceted role of AICD in the context of cancer. This is achieved by elucidating the dynamic interplay between systemic and cellular ATP

homeostasis, deciphering the intricate mechanisms governing AICD, elucidating its intricate involvement in cancer signaling pathways, and scrutinizing validated key genes. Moreover, the exploration of AICD as a potential avenue for cancer treatment underscores its essential role in shaping the future landscape of cancer therapeutics.

Key Words: Adenosine triphosphate induced cell death; Adenosine triphosphate homeostasis; Mechanism; Cancer signaling pathways; Prognosis and clinical values; Cancer treatment

Core Tip: The research delves deeply into the pivotal realm of adenosine triphosphate (ATP)-induced cell death (AICD), a fundamental cellular phenomenon that has captured significant scholarly interest owing to its pertinence in cancer biology and therapeutic strategies. Our review is dedicated to delivering an all-encompassing grasp of the intricate mechanisms underpinning AICD and its far-reaching ramifications within the cancer context. By meticulously dissecting the dynamic interplay between systemic and cellular ATP homeostasis, unraveling the governing mechanisms steering AICD, and probing its intricate entanglement with cancer signaling pathways, we present an exhaustive framework that illuminates the multifaceted role of AICD in the realm of cancer.

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INTRODUCTION

In recent years, adenosine triphosphate (ATP) induced cell death (AICD) has emerged as a discernible mode of cell death triggered by elevated extracellular ATP (eATP) levels, exhibiting intimate association with the progression of various cancer types[1-3]. ATP, or adenosine triphosphate, a nucleotide crucial for cellular energy metabolism, assumes a pivotal role in multiple tumor-related signaling pathways and biological processes[4,5]. Nonetheless, the precise mechanisms and modalities underlying AICD have long remained elusive. Subsequent investigations have unveiled the distinctive features and regulatory mechanisms of AICD, setting it apart from other forms of cell demise such as apoptosis and necrosis. This review provides a concise summary of key discoveries in the field of AICD that have propelled advancements (Figure 1)[5-12].

The identification of AICD represents a significant milestone in the realm of cell biology. Initially, researchers noted that the addition of exogenous ATP to cells resulted in cell death, thereby generating considerable interest and instigating extensive investigations[1]. AICD, being an inevitable facet of the cell's life cycle, assumes a pivotal role in maintaining tissue homeostasis and functionality, holding profound significance for tissue development, as well as the etiology and progression of various diseases. The mechanisms and specific manifestations of AICD remain unknown.

In the realm of oncology, aberrant regulation of AICD is a crucial determinant in tumor initiation and progression. It exerts direct influence on the fate of tumor cells, impeding their proliferation, invasion, and metastasis, while also indirectly suppressing tumor development through immune system activation[13-15]. Furthermore, AICD elicits transformative changes in the tumor microenvironment, having an impact on the proliferative, invasive, and migratory capabilities of tumor cells. Consequently, an extensive exploration of the interconnections and correlations between AICD and cancer provides novel targets and strategies for cancer therapy, facilitating a profound comprehension of the mechanisms underlying cancer onset and progression.

This paper presents a comprehensive review of the mechanisms underlying AICD and its association with cancer. The primary objective is to outline potential avenues for future research, investigating various aspects related to AICD and its relevance to cancer. Through an in-depth exploration of these mechanisms and their functions , this paper aspires to unveil novel breakthroughs in cancer treatment development and to enhance our comprehension of the occurrence and progression of cancer.

SYSTEMIC AND CELLULAR ATP HOMEOSTASIS

ATP homeostasis in biological systems and cells is a dynamic state of balance that involves the precise regulation of ATP concentration within a specific range. This is achieved through intricate processes including ATP synthesis, degradation, transport, and exchange both within and outside the cell, as well as regulation by the intracellular environment. Maintaining ATP homeostasis is crucial for sustaining cellular energy metabolism and overall physiological function. Various external factors can impact ATP production and stability, thereby perturbing ATP homeostasis.

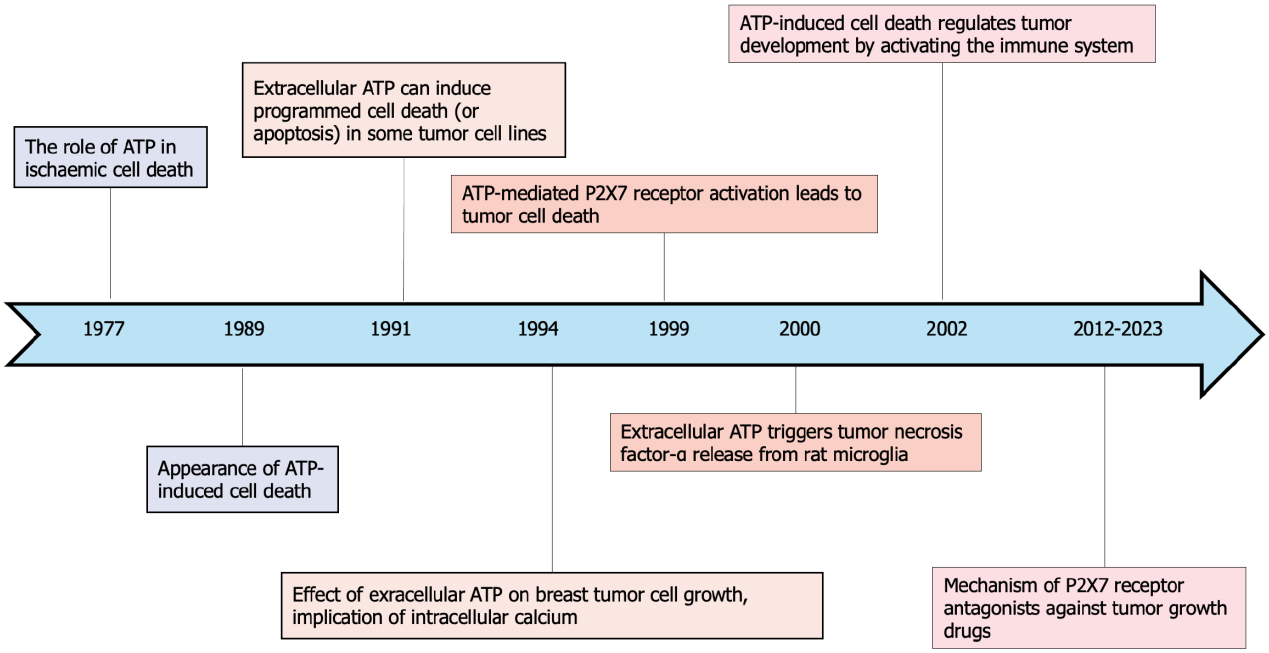

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Figure 1 Chronological depiction of key milestones in the exploration of adenosine triphosphate induced cell death. ATP: Adenosine triphosphate.

These factors encompass fluctuations in oxygen levels, alterations in nutrient availability, exposure to toxins and pharmacological agents, variations in temperature and thermal stress, changes in potential of hydrogen (pH), activation of inflammatory and immune responses, oxidative stress resulting from the accumulation of reactive oxygen species, infections and pathogen invasions, exposure to environmental toxins, as well as prolonged or intense physical and psychological stressors. Internally, several factors participate in the regulation of ATP homeostasis. This includes the coordinated regulation of ATP synthesis pathways, ATP consumption pathways, ATP transport pathways, and ATP hydrolase activity. Additionally, ATP homeostasis can be affected by disruptions in intracellular ATP leakage, alterations in eATP transport pathways, and dysregulation of eATP metabolic pathways (Figure 2).

EXTERNAL FACTORS THAT AFFECT ATP HOMEOSTASIS IN SYSTEMS AND CELLS

Hypoxia induces an elevation in eATP levels, which can be attenuated by the administration of L-type Ca^{2+} channel blockers and reduced by the activity of a nucleoside hydrolase such as apyrase. Furthermore, the application of iberiotoxin (100 nM), a specific blocker of O^{2-}sensitive Ca^{2+}-dependent K^+ channels, has been shown to enhance the release of ATP[16]. Nutrient deficiency also affects ATP synthesis and metabolism[17].

Chemotherapeutic agents trigger the release of ATP through two main mechanisms: Caspase-gated pannexin-1 (Panx1) channels and caspase/Panx1-independent pathways. Various pro-apoptotic drugs, such as topoisomerase II inhibitors, kinase inhibitors, and proteomic inhibitors, induce the functional activation of Panx1 channels by inhibiting the C-terminal cleavage of Panx1 mediated by caspase-3. The activation of caspase-activated Panx1 channels facilitates the efflux of ATP, as well as adenosine diphosphate (ADP) and adenosine monophosphate (AMP), which collectively constitute over 90% of the adenine nucleotide pool released during the transition from early to late apoptosis[18].

Blood flow undergoes a substantial increase in response to elevated temperatures, most likely attributed to physiological mechanisms governed by temperature-sensitive regulatory processes. ATP exhibits sensitivity to physiological temperature elevations observed both *in vitro* and in vivo, potentially as a result of the activation of cystic fibrosis transmembrane conductance regulator (CFTR)-like channels that disrupt ATP synthesis and stability[19]. Brainstem astrocytes possess the capacity to directly perceive alterations in blood and brain carbon dioxide and pH levels, and potentially govern the function of respiratory neuronal networks to modulate respiration. The reduction in extracellular pH triggers the release of ATP, which results in the depolarization of neighboring astrocytes and neurons. Perturbations in acid-base equilibrium can impede the regular progression of intracellular energy metabolism and impact ATP synthesis and stability[20]. Clodronate, as a highly effective and specific inhibitor of vesicular ATP release, represents a distinctive therapeutic approach to the management of chronic pain. Its inhibitory action on vesicular ATP release implicates its potential efficacy in the treatment of various purinergic-mediated disorders, such as inflammatory conditions, diabetes, and neurological ailments.

These discoveries underscore the contribution of chronic inflammation and immune responses to the dysregulation of cellular ATP homeostasis[21]. These findings imply that hydrogen peroxide triggers the release of ATP from intracellular compartments into the extracellular milieu *via* lysosomal exocytosis. The generation of reactive oxygen species during

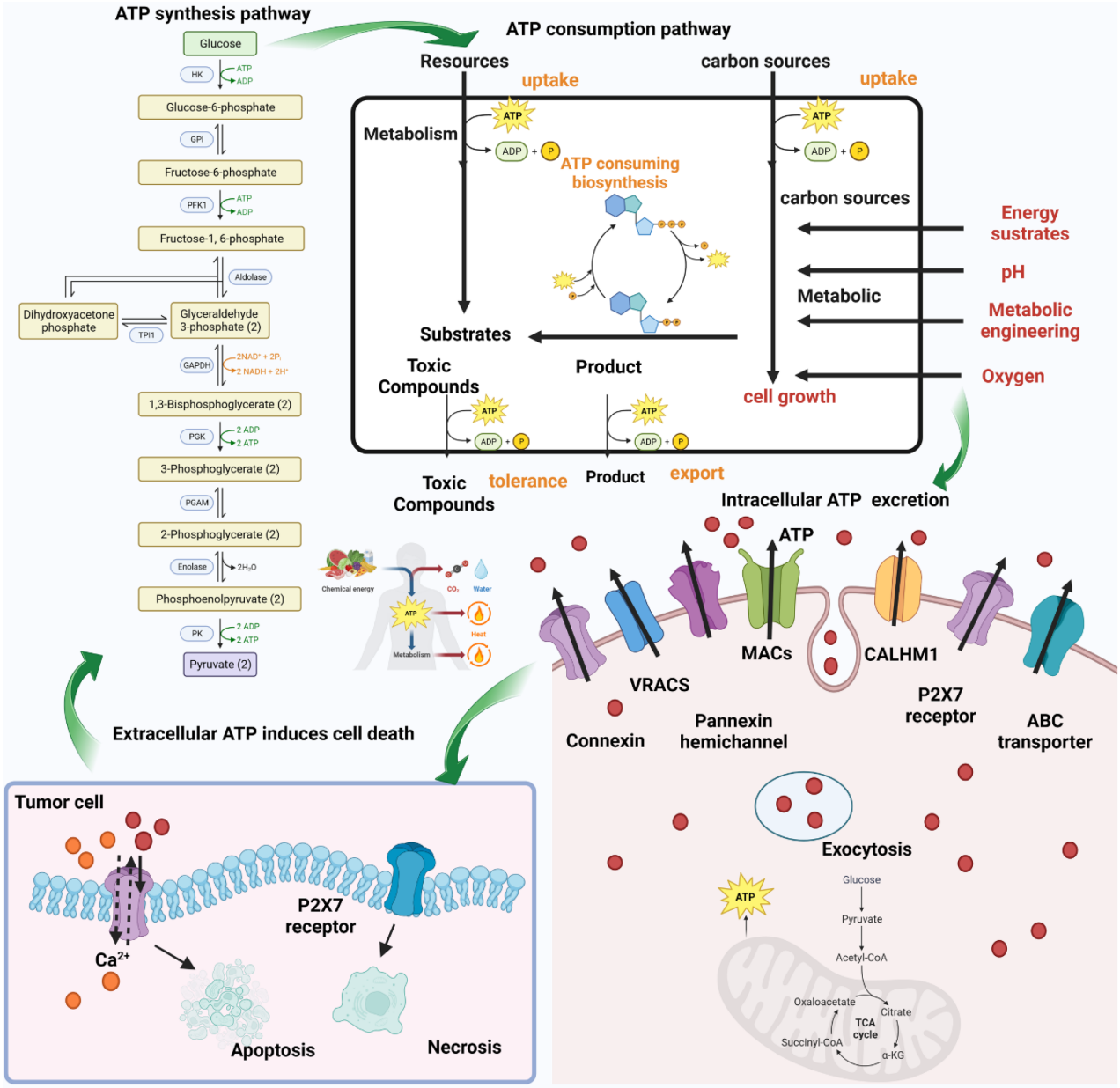

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Figure 2 The process of adenosine triphosphate production necessitates the sequential progression through a series of reactions encompassing glycolysis, pyruvate decarboxylation, the krebs cycle, and the respiratory chain. Cellular entities harness carbon sources to generate adenosine triphosphate (ATP) *via* glycolysis and the respiratory chain. Engineered cellular systems, when designed along specific pathways to facilitate targeted product synthesis, incur heightened ATP consumption for processes such as sugar uptake, cellular proliferation, biosynthesis, product efflux, and the acquisition of tolerance to cytotoxic agents. Furthermore, the equilibrium of ATP is influenced by a range of factors, including pH levels and oxygen availability. Perturbations in these dynamics can result in the overproduction of intracellular ATP, leading to its efflux through membrane-associated signaling channels or extracellular vesicles. Subsequent activation of cell membrane-associated P2 receptors by extracellular ATP triggers the influx of intracellular calcium ions, culminating in apoptotic cell demise. ATP: Adenosine triphosphate.

oxidative stress disrupts the delicate balance of ATP homeostasis[22]. Accumulating evidence suggests that the ATP/P2X7 signaling pathway confers extensive protection against viral infections in the host. The eATP exerts inhibitory effects on the replication of various viruses, including vesicular stomatitis virus, Newcastle disease virus, mouse leukemia virus, and herpes simplex virus, both *in vivo* and *in vitro*, by activating P2X7 receptors [P2X7R/purinergic receptor P2X7 (P2X7Rs)]. Concurrently, ATP administration leads to a significant upregulation of interferon-beta (IFN-β) expression in a concentration- and time-dependent manner. Mechanistically, ATP stimulates the secretion of IFN-β through the activation of the (p38 mitogen-activated protein kinase/c-jun n-terminal kinase/activating transcription factor 2) P38/JNK signaling pathway, which plays a crucial role in facilitating antiviral immune responses[23]. Furthermore, cellular energy homeostasis, particularly ATP production and stability, can be disrupted by environmental toxins (*e.g.*, heavy metals, organic pollutants) and prolonged or heightened stress. These external factors can disrupt the delicate balance of energy metabolism within cells, leading to alterations in ATP synthesis and stability[24,25].

INTERNAL FACTORS AFFECTING ATP HOMEOSTASIS IN SYSTEMS AND CELLS

The ATP synthesis pathway exerts a considerable influence on the cellular release of ATP. Oxidative phosphorylation and photophosphorylation, catalyzed by F1F0-ATP synthetase, represent the fundamental mechanisms by which cells generate energy through ATP synthesis[26]. Enhanced enzymatic activity of F1F0-ATP synthetase results in increased ATP production. Mitochondrial exposure to shear stress induces mitochondrial ATP production *via* the involvement of a specific protein called fossa or fossa protein-1, thereby converting the mechanical shear stress into a novel modulator of ATP production. This process leads to the release of ATP from vesicles and initiates purinergic Ca^{2+} signaling[25]. These findings indicate that under conditions of metabolic activity or stress, the ATP synthesis pathway can be activated in response to mitochondrial dysfunction, resulting in an upregulation of ATP production. Additionally, aberrant ion channels[27], transporters, and membrane vesicles can also contribute to augmented ATP synthesis in cells, thereby increasing the pool of available ATP for subsequent release.

Furthermore, the ATP-consuming pathway plays a crucial role in the release of ATP by cells. Cell proliferation, for instance, is associated with heightened ATP consumption[28]. In muscle protein synthesis, citrulline has been shown to induce ATP redistribution, resulting in increased ATP consumption during the process[29]. As a consequence, cells release more ATP to fulfill their heightened energy demands. Similarly, during the shortening of rabbit psoas muscle skin fibers, ATP consumption is elevated[30]. Studies have also demonstrated that certain abused drugs, such as degeneration of optic atrophy, exhibit increased ATP consumption during their transport across filter-grown CACO-2-monolayers[31]. ATPase and ATP-dependent enzyme reactions are implicated in this increased ATP consumption, which subsequently affects the quantity of ATP released by cells. These findings underscore the significance of the ATP-consuming pathway in modulating ATP release dynamics in cellular processes.

ATP transport channels play a vital role in cellular ATP release. Notably, the opening of the Panx1 half-channel is modulated by the activity of P2X7Rs. Evidence suggests that P2X7Rs are activated under pathological conditions like ischemia, leading to the opening of the PANX1 half-channel. This allows substantial Ca^{2+} influx from the extracellular space and the release of ATP from the cytoplasm, ultimately triggering cell death[32]. These findings indicate that activated Pannexin channels facilitate ATP release from the intracellular space through the cell membrane to the extracellular environment.

CFTR also promote ATP release by stimulating independent ATP release channels, thus governing cellular autocrine signaling[27]. Studies have demonstrated that CFTR forms pores in the cell membrane, enhancing the efflux of ATP from the cytoplasm to the extracellular milieu. Furthermore, eATP plays a regulatory role in various signaling systems, including the propagation of intercellular Ca^{2+} signaling (ICS). Nexin semi-channels, P2X7Rs, pannexin channels, anion channels, vesicles, and transporters are recognized as potential ATP-released channels; however, their precise contributions to ICS remain subject to debate. In the inner ear, these connexins play a dual and crucial role in Ca^{2+} signaling: serving as semi-channels, they promote ATP release and sustain long-range ICS propagation; acting as gap junction channels, as well as facilitating the diffusion of Ca^{2+}-mobilized second messengers among coupled cells[33]. Additionally, the binding of ATP facilitates the release of substrates by multidrug resistant protein [34]. Simultaneously, multidrug-resistant protein participates in intracellular substance transport and excretion, contributing to the transport of ATP from the cytoplasm to the extracellular space, thus promoting ATP release.

Cells can regulate the balance of ATP concentration inside and outside the cell by modulating the activity of ATP hydrolase. Among the ATP hydrolases, exonucleoside triphosphate diphosphate hydrolases form a significant enzyme family, with members including ectonucleoside triphosphate diphosphohydrolase 1 (CD39) and ENTPD3. These enzymes are capable of catalyzing the hydrolysis of ATP to ADP, leading to the degradation and subsequent release of ATP[35]. Moreover, the ectonucleotide pyrophosphatase/phosphodiesterase family includes members such as ectonucleotide pyrophosphatase/phosphodiesterase 1 and ectonucleotide pyrophosphatase/phosphodiesterase 2, which are also involved in ATP hydrolysis. These enzymes catalyze the hydrolysis of ATP to AMP and two inorganic phosphate ions. The impact of eATP on the release of ATP from cells is a multifaceted and intricately regulated process that entails the interplay of various cell surface receptors, channels, and enzymes.

AICD MECHANISMS

The complexity of AICD can vary depending on the specific cell type and the surrounding microenvironment. Nevertheless, several general mechanisms have been elucidated. One of these mechanisms involves the activation of purinergic receptors, particularly the P2X7R, which can initiate a cascade of events leading to cell death. Another mechanism is associated with the elevation of intracellular calcium ion concentration. Moreover, ATP-triggered cell death may also contribute to the activation of inflammatory responses. Lastly, AICD is linked to the perturbation of mitochondrial function, with the release of cytochrome c being strongly associated with the activation of apoptosis signaling pathways (Figure 3).

EATP stimulates the activation of the P2X7R, leading to inflammasome activation and the release of pro-inflammatory cytokines in monocytes. Native-like T cells effectively respond to innate stimuli by secreting a multitude of pro-inflammatory cytokines, and human T cell compartments exhibit the highest expression of the P2X7R. Within the innate lymphoid population, Tγδ cells demonstrate heightened sensitivity to P2X7R activation compared to conventional T cells, influencing fundamental cellular mechanisms such as calcium signaling and AICD[36]. Neuroinflammation is positively linked to P2X7R activation through risk-associated molecular patterns, with eATP being the most prominent among them. The P2X7R is expressed in various retinal cells, including retinal endothelial cells, and ATP serves as the sole

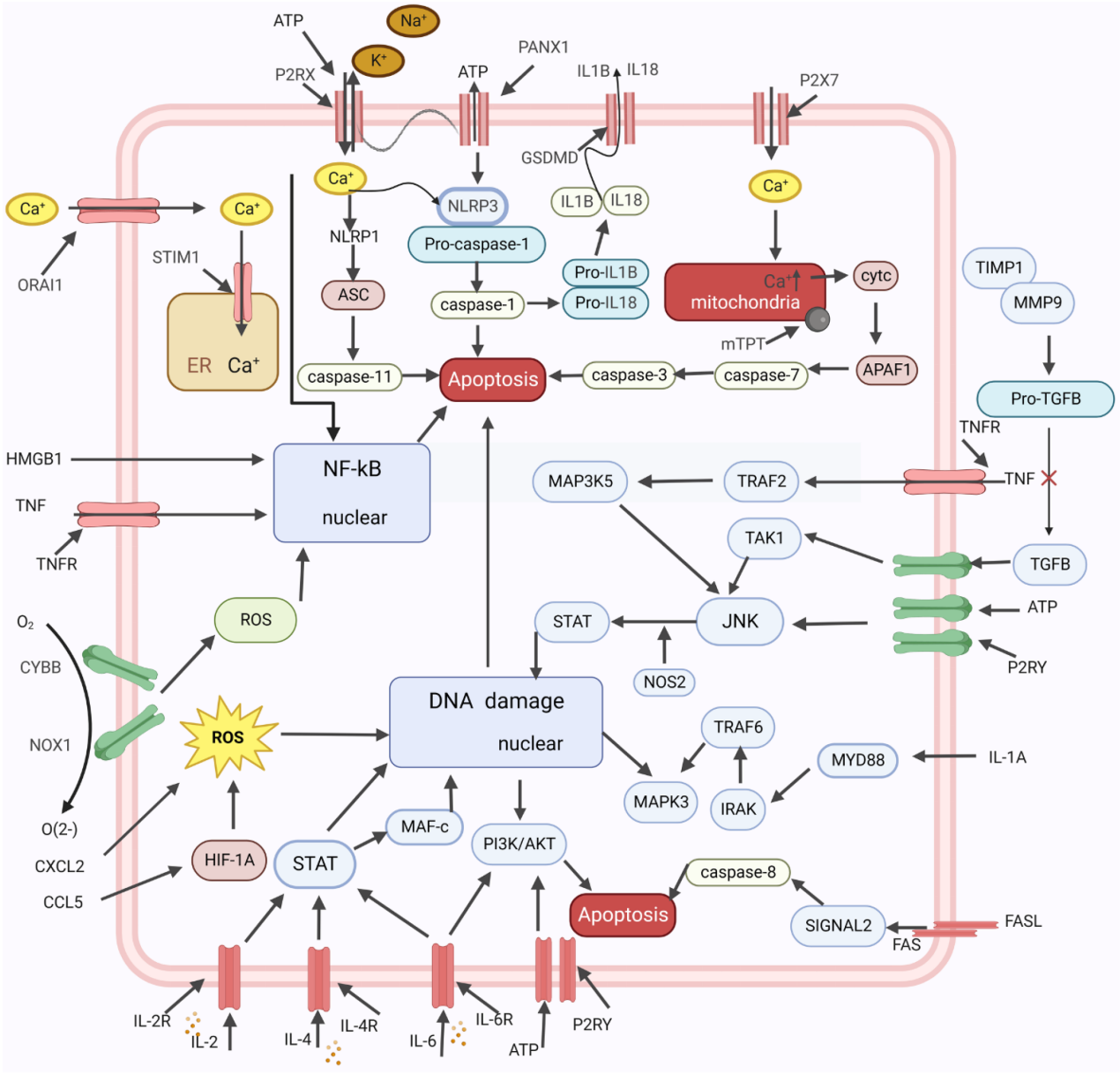

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Figure 3 Illustration of the mechanism of adenosine triphosphate induced cell death, which involves several interconnected pathways. Upon binding to the purinergic receptor P2X7 (P2X7R), extracellular adenosine triphosphate (ATP) induces a surge in intracellular calcium levels, leading to caspase activation and subsequent cell death. Additionally, ATP activates the NOD-like receptor family pyrin domain containing 3 inflammasome by releasing High Mobility Group Box 1/Toll-Like Receptor 4, triggering caspase-1 activation and promoting cell apoptosis. The interaction between ATP and P2X7Rs also activates the Nuclear Factor-kappa B and Phosphatidylinositol 3-kinase-protein kinase B/hypoxia-inducible factor pathways, resulting in DNA damage and cell death. Simultaneously, the continuous accumulation of intracellular Ca^{2+} stimulates the opening of the mitochondrial permeability transition pore, leading to DNA damage and ultimately cell necrosis. Ca^{2+} induces mitochondria to release cytochrome c, further contributing to the apoptotic process. Moreover, ATP-triggered cellular demise instigates a transformative shift within the extracellular microenvironment, concurrently unleashing a plethora of cytokines. Lastly, apart from elucidating the fundamental underpinnings of ATP induced cell death, this Figure also encapsulates a synthesized appraisal of the plausible mechanisms governing microenvironmental equilibrium, as extrapolated from relevant literature. ATP: Adenosine triphosphate; NF-κB: Nuclear Factor-kappa B; NLRP3: NOD-like receptor family pyrin domain containing 3; PI3K-AKT: Phosphatidylinositol 3-kinase-protein kinase B; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; ASC: Apoptosis-related speckle-like protein; STAT: Signal transducer and activator of transcription.

physiological agonist for P2X7. High glucose induces periretinal cell death by activating P2X7R, and the ATP released by the deceased cells functions as a "danger signal," further amplifying the inflammatory response caused by glucose-induced injury[37]. Research has demonstrated that brief (1-4 min) stimulation of mouse macrophages with high eATP leads to delayed (hourly) cell death, as evidenced by DEVDase (caspase-3 and caspase-7) activity. "Transient" P2X7R activation and Ca^{2+} overload have been identified as triggers for death in native mouse macrophages, independent of Panx1 and pro-inflammatory caspase-1 and toll-like receptor (TLR) signaling[38]. Furthermore, knockdown of chloride intracellular channel protein 4 enhances ATP-induced apoptosis of HN4 cells through mitochondrial and endoplasmic reticulum pathways[39].

AICD AND CANCER SIGNALING PATHWAYS

AICD is directly associated with multiple signaling pathways in tumor cells, achieved through the binding and activation of key molecules in these pathways. Among them, a correlation exists between the mitochondrial pathway and AICD. Upon eATP activation of the P2X7R, intracellular mitochondrial Ca^{2+} levels increase, leading to the formation of Bcl-2-associated X /Bcl-2 homologous antagonist/killer oligomer complexes that insert into the outer membrane pores of mitochondria. This causes changes in mitochondrial osmotic pressure and transmembrane potential loss, subsequently facilitating the release of cytochrome c from mitochondria into the cytoplasm and activating the caspase-9 precursor.

Consequently, caspase-3 and caspase-7 are activated, triggering a Caspase cascade reaction, and ultimately inducing cell apoptosis[40-47]. ATP promotes apoptosis by activating extracellular P2X7Rs. The apoptosis of tumor cells can induce apoptosis in surrounding cells, resulting in proliferative necrosis, providing an environment favorable for cancer spread. P2X7R activation leads to tumor necrosis factor (TNF) activation, stimulating Caspase activation, and initiating the execution phase of apoptosis[48,49]. Simultaneously, P2X7R activation alters membrane permeability, leading to an outflow of intracellular ions, cell swelling, and rupture, ultimately causing cell necrosis[50,51]. Necrosis is an internal tumor death that creates an ideal environment for cancer dissemination. ATP activates immune cell membrane P2X7Rs, triggering the release of necrosis factors, and activating serine-threonine kinases such as receptor-interacting protein kinase 1 and receptor-interacting protein kinase 3 after TNF receptor 1 or TLR stimulation, ultimately inducing necrosis [50-54].

The autophagy pathway plays a crucial role in recycling metabolic waste in tumor cells, ensuring their energy requirements are met, or facilitating evasion of apoptosis, ultimately leading to tumor cell proliferation. ATP can promote autophagy initiation by activating the AMP-activated protein kinase (AMPK) signaling pathway[55,56]. When intracellular ATP levels decrease, AMPK becomes phosphorylated and activated, subsequently activating the unc-51-like autophagy activating kinase 1 complex and initiating the autophagy process.

Nuclear factor kappaB (NF-κB) assumes a critical role in numerous biological processes of tumor cells, encompassing inflammation, proliferation, survival, apoptosis, angiogenesis, epithelial-mesenchymal transition (EMT), metastasis, stem-cell characteristics, metabolism, and therapeutic resistance. Prior investigations have established that NF-κB activation leads to DNA damage and initiates the signaling pathway of NF-κB[57]. The Wnt signaling pathway holds paramount significance in embryonic development by preserving stem cell properties and dictating cell fate. When ATP binds to the P2 purinergic receptor, it activates protein kinase C and phosphoinositide 3-kinase (PI3K) signaling pathways, thereby inhibiting the activity of glycogen synthesis kinase-3β (GSK-3β)[57-60].

Consequently, β-catenin is no longer phosphorylated and degraded by GSK-3β, which regulates cell growth and differentiation. Several studies have indicated that ATP can promote the activation of the PI3K/protein kinase B (Akt) pathway through P2 purinergic receptor activation. This process results in PI3K catalyzing the transformation of phosphatidylinositol diphosphate into phosphatidylinositol triphosphate (PIP3). Subsequently, PIP3 attracts Akt kinase to the cell membrane, resulting in its phosphorylation and activation. Activated Akt kinase modulates cancer development by phosphorylating a diverse array of downstream effector proteins.

MAPK comprises a cluster of evolutionarily conserved serine-threonine kinases, encompassing extracellular signal-regulated kinase (ERK), p38, JNK, and big mitogen-activated protein kinase 1, with each representing distinct classical MAPK pathways. ATP phosphorylates and activates MAPK protein kinases (such as ERK, JNK, and p38) by engaging P2 purinergic receptors[61].

Research has revealed that AICD may incite DNA damage, consequently activating tumor protein 53 (p53) expression and function. Activated p53 effectively regulates multiple target genes, including cyclin-dependent kinase inhibitor 1 (p21), Bax, p53 upregulated modulator of apoptosis, *etc.*, which are closely associated with cancer development[62,63]. The induction of AICD exerts a direct or indirect impact on cancer signaling pathways and cancer characteristics, thus further underscoring its vital role in cancer.

VALIDATED KEY GENES IN AICD KEY GENES: FUNCTIONS, PROGNOSIS, AND CLINICAL VALUES

The underlying mechanism of AICD remains incompletely understood. However, several overarching mechanisms have been revealed. Among them, a pivotal pathway involves the activation of the P2 receptor family, specifically the P2X7R, by eATP. Perturbation or activation of these genes may modify susceptibility to AICD. Furthermore, investigations into ATP homeostasis have highlighted the regulatory role of PANX1 protein in intracellular ATP concentration, thus influencing AICD. Also, activation of P2X7R triggers an elevation in intracellular calcium levels, which is balanced by the calcium release-activated calcium channel protein 1 (ORAI1) and stromal interaction molecule (STIM) 1 proteins to maintain intracellular calcium homeostasis. Besides these mechanisms, apoptotic and mitochondrial pathways also participate in AICD. Consequently, 37 genes have been identified as crucial players in the AICD mechanism. As the concept of AICD gains prominence, researchers are increasingly focusing on its role in diverse tumor types, implying that the expression levels and clinical significance of AICD may hold significant relevance across different tumors.

Therefore, this paper will discuss prevalent cancer types globally. Table 1 below enumerates the functions and subcellular localizations of these genes during AICD. Due to the limited availability of cancer prognosis-related information regarding AICD genes, an extensive analysis was conducted using clinical data from the database provided by the American Cancer Letters and Biology Institute (https://www.aclbi.com/static/index.html/). Table 1, establishes a comprehensive gene prognosis model centered on AICD, aiming to assess the prognostic significance of individual genes across several types of cancer.

Table 1 List of adenosine triphosphate induced cell death core genes and their relationship with tumors

Gene	Full name	Risk factor	Protective factor	Clinical prognostic value	Role in ATP induced cell death	Ref.
P2RX7	Purinergic receptor P2X7	NA	NA	HNSC, KIRC, LAML, SARC	Activates inflammatory mediators and increases calcium ions	Tamajusuku *et al* [89]
CASP3	Caspase-3	DPG, HNSC, MESO	OV, THYM	ACC, COAD, LGG, LIHC, LUSC, PAAD	Caspase-3 cleavage by caspase-1/4/5/11 forms pores, releasing pro-inflammatory cytokines	Souza *et al*[90]
PANX1	Pannexin-1	NSCLC, BRCA, RCA, SARC, MESO		LUAD, MESO, PAAD, STAD	P2X7 activation opens PANX1 channels, releasing ATP and triggering cell death pathways	Shoji *et al*[91]
NLRP3	NOD-like receptor family pyrin domain-containing protein 3	SARC, TGCT	PAAD	LAML, SKCM	NLRP3 activated by stimuli forms inflammasome, triggers caspase-1 activation, releases cytokines, induces apoptosis	Sadatomi *et et al* [92]
CASP1	Caspase-1	DPG, HNSC, PAAD, LAML, THYM	BRCA, MESO	BRCA, LAML, LGG, MESO, SARC, THYM	Caspase-1 induces cytokine processing, pyrosis, and inflammation	Sadatomi *et al*[92]
P2RY1	P2Y purinoceptor 1	DPG, PAAD	NA	BLCA, KIRC	P2RY1 can increase calcium ions in the Golgi apparatus	Ohishi *et al*[93]
P2RY11	P2Y purinoceptor 11	NA	HNSC,PAAD,UCEC, Rb, TGCT	ACC, BLCA, LGG, UCEC, UVM	Involved in immune inflammatory mechanisms	Yoon *et al*[94]
ORAI1	Calcium release-activated calcium channel protein 1	RCA, SARC, MESO	HNSC	ACC, BLCA, KIRP, LGG, MESO,	Increased intracellular calcium ions	Peng *et al*[95]
STIM1	Stromal interaction molecule 1	HNSC, PCPG	SARC	KIRP, PAAD, UVM	STIM1 responds to ATP-induced calcium influx, activating ORAI1 and promoting cell death	Peng *et al*[95]
CASP8	Caspase-8	CESC, RCA	DPG, BRCA, OV, SKCM, SARC	LGG, PAAD, SKCM	CASP8 causes apoptosis	Zeng *et al*[96]
CASP9	Caspase-9	DPG, NSCLC, ACC, THYM	PAAD,BRCA, Rb, MESO	ACC, BLCA, BRCA, LAML, LGG, MESO	CASP9 causes apoptosis	Zeng *et al*[96]
CASP7	Caspase-7	HCC, THYM	BRCA, MESO	ACC, KIRC, LGG, LIHC, STAD	CASP7 causes apoptosis	Zeng *et al*[96]
P2RX3	Purinergic receptor P2X3	DPG	PAAD,NSCLC, CESC, Rb	KIRC, KIRP, LUAD	NA	Ohishi *et al*[93]
NLRP1	NLR family pyrin domain-containing protein 1	RCA, MESO, THYM	HNSC, NSCLC, SARC	LGG, LUAD, SKCM	NLRP1 activates caspase-1, induces pyrodeath, and releases IL-1β and IL-18	Zhao *et al*[97]
P2RX4	P2X purinoceptor 4	HNSC, HCC, RCA, Rb, MESO	DPG, UCEC	LGG, LIHC, MESO, UCEC, UVM	P2RX4 contributes to AICD (pyroptosis) by activating the NLRP3 inflammasome, leading to IL-1β and IL-18 production	Ohishi *et al*[93]
P2RX5	P2X purinoceptor 5	RCA, ACC	HNSC	ACC, KIRC, LGG, SKCM	NA	Ohishi *et al*[93]
SAPK	Stress-Activated Protein Kinase	NA	NA	NA	ATP induces cell death *via* SAPK pathways, regulating apoptosis, necrosis, and stress	Humphreys *et al* [98]

					signaling	
p38 MAPK	p38 mitogen-activated protein kinases (p38 MAPK)	NA	NA	NA	ATP activates p38 MAPK, which leads to cell death through apoptosis and necrosis	Noguchi *et al*[99]
ASK1	Apoptosis Signal-Regulating Kinase 1	OV, THYM	DPG, HNSC, RCA	KIRC, LAML, LGG, MESO, PAAD, READ, SKCM	Excessive ATP induces cellular stress, activating ASK1 and downstream pathways for cell death	Noguchi *et al*[99]
NOX2	NADPH oxidase 2	NA	NA	CESC, KIRC, LIHC, LUAD, SKCM	ATP activates NOX2, generating ROS causing oxidative stress and potential cell death	Noguchi *et al*[99]
bax	BCL2 Associated X	NA	PAAD, BRCA, CESC, RCA	LGG, LIHC, MESO, SKCM, UVM	Excessive ATP triggers BAX activation, mitochondrial dysfunction, and apoptotic cell deat	Wen *et al*[100]
MLC	Myosin Light Chain	UCEC, MESO	HNSC, PAAD, BRCA, CESC, RCA, PCPG	CESC, KIRC	ATP depletion hampers muscle contraction, affecting myosin function and cellular viability	Hwang *et al*[101]
ROCK I	Rho-associated, coiled-coil containing protein kinase 1	THYM	BRCA, RCA	KIRC, LGG, PAAD	ATP activates P2X7 receptors, inducing apoptosis *via* the Rho/ROCK pathway, potentially involving ROCK I	Hwang *et al*[101]
ERK1/2	Extracellular Signal-Regulated Kinase 1 and 2	NA	NA	NA	ERK1/2 promotes cell survival or antagonizes apoptosis, but prolonged activation may lead to cell death. Activates the ERK1/2 pathway, affecting cell fate	Tsukimoto *et al* [102]
P2X6	P2X purinoceptor 6	DPG, HNSC, BRCA, OV, UCEC, RCA, MESO	SARC, ACC	ACC, HNSC, KIRC, LGG, OV, UVM	Activation may raise calcium levels, potentially triggering cell death	Banfi *et al*[103]
CYTC	Cytochrome c	HNSC, NSCLC, Rb, MESO, THYM	DPG, RCA	ACC, BRCA, COAD, HNSC, KIRP, LAML, LGG, LUAD, MESO, UCEC	Cytochrome c released by mitochondria during cell stress triggers cell apoptosis	Sadatomi *et al*[92]
TNF-α	Tumor necrosis factor alpha	CESC, Rb, MESO	HNSC, PAAD, RCA, SARC	SKCM, THYM	ATP induces cell death, activating TNF-α and triggering apoptosis or necroptosis pathways. Immune cells produce TNF-α in response to ATP, amplifying the cellular response	Hide *et al*[5]
P2RY5	P2R purinoceptor 5	NA	NA	NA	NA	Yoon *et al*[94]
P2RY14	P2R purinoceptor14	RCA	HNSC, HCC, OV, UCEC MESO	HNSC, KIRP, LUAD, SKCM, UCEC	NA	Ohishi *et al*[93]
P2RY13	P2R purinoceptor 13	NA	PAAD, NSCLC, CESC, SKCM, RCA, SARC	ACC, CESC, KIRC, LUAD, SARC, SKCM, UCEC	P2Y13 may play a role in ADP receptors, mainly involved in ATP homeostasis	Ohishi *et al*[93]
P2RY12	P2R purinoceptor 12	DPG,PAAD,OV, SARC, MESO, THYM,	NSCLC	LAML, LUAD, SKCM	P2Y12 may play a role in ADP receptors, mainly involved in ATP homeostasis	Ohishi *et al*[93]
P2RY6	P2R purinoceptor 6	DPG, HNSC, PAAD, HCC, BRCA, RCA	SARC,	KIRC, LGG, SKCM, UVM	P2Y6 may be involved in calcium signaling	Ohishi *et al*[93]

					leading to cell death	
P2RY4	P2R purinoceptor 4	HCC, SARC	HNSC, PAAD, RCA	PRAD	P2Y6 may be involved in calcium signaling leading to cell death	Ohishi *et al*[93]
P2RY2	P2R purinoceptor 2	DPG, UCEC, BRCA, OV	RCA, SARC	BLCA, GBM, LAML, LGG, MESO, OV, PAAD, UCEC, UVM	ATP binding triggers intracellular signaling pathways that may lead to cell death	Ohishi *et al*[93]
ANO6	Anoctamin-6	HNSC, PAAD, OV, NSCLC, BRCA, CESC		BRCA, CESC, KIRC, LGG, MESO, OV, PAAD	As a calcium-activating channel and superburning enzyme, it may influence cell death pathways	Ousingsawat *et al*[104]
cyclinE2	cyclinE2	DPG, HCC, UCEC, RCA, SARC, Rb, ACC, MESO	HNSC	ACC, BRCA, KICH, KIRP, LGG, LIHC, LUAD, MESO, THYM	NA	Wang *et al*[105]
cyclinD2	Cyclin D2	HNSC	PAAD, NSCLC, BRCA, LAML, MESO, PCPG	LAML, LGG, LUSC, MESO, PAAD, SKCM, THCA, UCEC	NA	Wang *et al*[105]

ACC: Adrenocortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; COADREAD: Colon adenocarcinoma/rectum adenocarcinoma esophageal carcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; GBMLGG: Glioma; HNSC: Head and neck squamous cell carcinoma; KICH: Kidney chromophobe; KIPAN: Pan-kidney cohort (KICH + KIRC + KIRP); KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Brain lower grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; MESO: Mesothelioma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcomav; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; STES: Stomach and esophageal carcinoma; GCT: Testicular germ cell tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; UVM: Uveal melanoma.

AICD IN GLOBALLY-PREVALENT CANCER TYPES

Breast cancer

Breast cancer is the predominant malignancy among women globally, holding the foremost position in cancer-related mortalities. Emerging investigations have revealed a significant elevation of P2X7Rs in breast cancer, implicating their involvement in mediating crucial cellular processes. Specifically, P2X7Rs have been associated with the activation of the Akt signaling pathway, the calcium-activated small conductance calcium-activated potassium channel 3 potassium channel, and the induction of EMT. Additionally, they play a regulatory role in the secretion of extracellular vesicles, thereby fostering breast cancer invasion and migration. These mechanisms are influenced by factors such as hypoxia and ATP exposure[64]. In T47D cells, the silencing of the P2X7R remarkably hindered the invasion and migration induced by ATP stimulation. Moreover, the activation of P2X7Rs by ATP led to a down-regulation of E-cadherin protein levels and an up-regulation of matrix metalloproteinase-13 (MMP-13) production[65]. This suggests that ATP-induced activation of P2X7Rs may facilitate breast cancer cell invasion and migration through the activation of the Akt pathway and the regulation of E-cadherin and MMP-13 expression. Furthermore, the glycoprotein PANX1 has emerged as a key player in breast cancer metastases, bearing similarities in structure and function to connexins and contributing to cell-environment communication. Elevated PANX1 expression has been associated with a shift towards an EMT phenotype and has been implicated in the tumor-promoting role of breast cancer, correlating with unfavorable clinical outcomes in breast cancer patients[66].

The expression levels of ORAI1 were also found to be upregulated in breast cancer cell lines. Employing ORAI1 small interfering RNA (siRNA) interference in breast cancer cells resulted in reduced calcium ion entry related to storage operations and altered calcium inflow linked to invasive stimulation. Microarray data analysis of 295 breast cancer cases indicated that the transcriptional breast cancer subtype with the worst prognosis (basal type) exhibited alterations in the relationship between ORAI1 regulatory factors, namely STIM1 and STIM2. Notably, breast cancer patients with tumors expressing high levels of STIM1 and low levels of STIM2 had significantly worse prognoses[67]. *In vitro* investigations have further validated the pivotal role of STIM1 in the proliferation and metastasis of breast cancer. STIM1 was found to be expressed in 66.1% of breast cancer cases, a significantly higher proportion than in adjacent non-tumor tissues. Moreover, STIM1 overexpression demonstrated positive associations with larger tumors, lymph node metastasis, and negative estrogen receptor status. Additionally, in breast cancer patients, increased STIM1 expression was significantly linked to poorer disease-free survival but did not exhibit a significant correlation with overall survival[68].

The P2Y2 receptor plays a pivotal role in the progression of various tumor types. It exhibits high expression levels in MCF7 and Hs578T breast cancer cells. Targeting the P2Y2 receptor with siRNA leads to a significant attenuation of ATP- or uridine 5′-triphosphate-driven migration and invasion of breast cancer cells, along with down-regulation of the EMT-related genes snail family transcriptional repressor 1 and E-cadherin. Consistent with *in vitro* findings, the expression of the P2Y2 receptor was markedly higher at the tumor infiltrating margin, invasive tumor cells within breast adipose tissue, and/or cancer embolus of lymphatic sinus compared to the tumor core[69]. Abnormal expression and mutations of the P2Y6 receptor have been observed in most tumor types and strongly correlated with poor prognosis in breast cancer patients. Additionally, uridine diphosphate significantly enhances the migration and invasion of breast cancer cells, and this effect can be blocked by P2Y6 receptor-specific inhibitors MRS2578 and P2Y6 short hairpin RNA (shRNA)[70]. Furthermore, the expression of P2Y12 is significantly up-regulated in cisplatin-treated 4T1 breast cancer cell lines. The combined use of P2Y12 inhibitors and cisplatin significantly enhances the cytotoxic response of 4T1 cancer cells[71]. Notably, a certain relationship exists between AICD and breast cancer. Being an intracellular energy molecule, ATP plays critical biological functions within the cell. Therefore, further investigations are warranted to elucidate the mechanism of action and potential therapeutic value of ATP in breast cancer.

Lung cancer

Lung cancer, one of the most prevalent cancer types globally, is directly associated with smoking, but it can also affect non-smokers. It involves the uncontrolled proliferation of lung cells, leading to the formation of malignant tumors. Recent research has demonstrated a significant relationship between the dysregulated expression of the P2X7R and the occurrence and progression of lung cancer. Particularly, the P2X7R is prominently expressed in tumor-associated macrophages (TAMs), and its deficiency impairs the "M2-like" polarization of TAM by reducing the phosphorylation of signal transducer and activator of transcription 6 and interferon regulatory factor 4. Consequently, P2X7 deficiency curtails lung cancer and Lewis lung cancer progression by inhibiting tumor cell proliferation and angiogenesis, promoting T cell mobilization, and reverting M2-like TAM polarization[72]. Furthermore, relevant data has verified the functional presence of P2X1, P2X4, and P2X7Rs in laboratory of allergic disease 2 cells and HLMC[73].

Overexpression of ORAI1/calcium release activated calcium modulator 1 (CRACM1) has a suppressive effect on extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt phosphorylation. This overexpression induces the expression of the cell cycle regulator p21 while reducing the expression of cyclin D3. As a result, cell cycle arrest occurs in the G0/G1 phase. Of particular significance is that the heightened expression of ORAI1/CRACM1 significantly diminishes epidermal growth factor-triggered calcium influx[74]. In non-small cell lung cancer (NSCLC), the expression of STIM1 is substantially elevated compared to benign lesions and is positively correlated with advanced T stages of NSCLC. STIM1 knockdown in NSCLC cell lines A549 and lung cancer (SK-MES-1) Leads to significant inhibition of cell proliferation and arrests A549 and SK-MES-1 cells in the G2/M and S phases of the cell cycle. Moreover, STIM1 knockdown markedly reduces the growth of xenografted tumors in nude mice[74,75].

While some studies have indicated the potential involvement of ATP in the regulation of lung cancer occurrence and development, further research is needed to confirm and clarify whether ATP acts as an independent risk factor for lung cancer. Additionally, exploring how ATP-related mechanisms can be applied for clinical intervention remains an essential area of investigation.

Colorectal cancer (CRC)

CRC stands as a prominent contributor to cancer-related mortality on a global scale. In CRC patients, distinct phenotypes characterized by high and low P2X7R expressions have been identified. Those exhibiting high P2X7R expression displayed shorter survival, elevated serum carcinoembryonic antigen levels, and more advanced tumor stages. Moreover, P2X7R expression showed significant upregulation in metastatic CRC and metastatic CRC cell lines, indicating a positive correlation between P2X7R expression and metastasis[75,76]. P2X7R, through inducing glucose transporter protein 1 (GLUT-1) expression, aids in tumor cells' resistance to unfavorable conditions. GLUT1, a principal glucose transporter in CRC cells, serves as a prognostic marker for adverse outcomes in CRC patients. Recent investigations have identified P2X7R and GLUT-1 as potential prognostic biomarkers for the development of novel treatment strategies. Higher P2X7R expression was found in patients with poorly differentiated tumors, and those with GLUT-1 overexpression experienced reduced overall survival and disease-free survival. Therefore, P2X7R and GLUT-1 may independently serve as prognostic markers, offering a novel avenue for targeted therapy in CRC patients[77].

Purinergic receptors, particularly P2Y2 receptors, have been identified to exert an anti-apoptotic effect in ursolic acid-induced CRC HT-29 and prostate cancer DU145 cells. P2Y2 receptor activation leads to Src activation, subsequently phosphorylating p38, resulting in cyclooxygenase-2 (COX-2) overexpression and thereby inducing resistance to apoptosis in HT-29 and DU145 cells[78]. Current investigations indicate that sustained activation of P2Y6R may contribute to the development of intestinal tumors by inhibiting the apoptotic process and promoting chemotherapy resistance, which poses a critical challenge in the management of CRC patients[79].

STIM1 overexpression is prevalent in CRC patients. Notably, elevated STIM1 expression is significantly associated with tumor size, depth of invasion, lymph node metastasis, and serum carcinoembryonic antigen levels in CRC. Furthermore, ectopic STIM1 expression enhances the motility of CRC cells, while STIM1 depletion through shRNA inhibits CRC cell migration[80]. Additionally, ORAI1 is upregulated in human CRC tissues, and its high expression is closely linked to tumor invasion depth, lymph node metastasis, and peri-nerve invasion. Patients with high ORAI1 expression experience shortened overall survival. CRC cell lines also exhibit upregulated ORAI1 expression. Although ORAI1 downregulation suppresses cell proliferation, this growth inhibition is not attributed to augmented apoptosis, and STIM1 does not participate in the regulation of CRC cell proliferation[81].

Prostate cancer

Prostate cancer, one of the most prevalent malignancies in men, is characterized by the aberrant proliferation and propagation of malignant cells within prostate tissue. In the context of prostate cancer, the expression profile of P2X7R exhibits a distinctive stage-specific pattern, initially appearing in the nucleus, progressing to the cytoplasm, and ultimately localizing to the apical membrane of epithelial cells. Early biopsy findings revealed that all 114 prostate tissues examined exhibited positive P2X7 staining, indicating the presence of P2X7 at the early stage of prostate cancer[82]. Subsequent investigations demonstrated that the downregulation of P2X7 by siRNA substantially attenuated the *in vitro* migration and invasion of prostate cancer cells driven by ATP or 2′,3′-O-(Benzoyl-4-benzoyl)-adenosine 5′-triphosphate, while also suppressing tumor invasion and metastasis in nude mice. Additionally, the silencing of P2X7 significantly reduced the expression of EMT/invasion-related genes, namely Snail, e-cadherin, claudin-1, interleukin (IL)-8, and matrix metalloproteinase-3, along with dampening the phosphorylation of PI3K/AKT and ERK1/2[83].

Moreover, P2X4 protein exhibits expression in prostate epithelial cells, a specific subset of CD66+ neutrophils, and the majority of CD68+ macrophages. Elevated P2X4 expression in prostate cancer has been associated with post-radical prostatectomy metastasis. Depletion of the P2X4 gene leads to a reduction in the growth, migration, and invasion of prostate cancer cells. Furthermore, knockout of P2X4 in Myc-CaP cells results in a significant decrease in the subcutaneous growth of allografts in FVB/NJ mice[84]. Additionally, other investigations have demonstrated that indoline derivatives can activate the P2Y1R receptor and induce mitochondrial apoptosis signaling[85]. In prostate cancer cells, the P2Y2 receptor shows a notable expression. Suppression of the P2Y2 receptor inhibits cell invasion and metastasis. Moreover, ATP presence promotes the expression of IL-8 and Snail genes while inhibiting the expression of E-cadherin and Claudin-1. Consequently, knockdown of the P2Y2 receptor affects the expression of these EMT/invasion-related genes both *in vitro* and *in vivo*[86].

The functional interplay between STIM1 and ORAI1, as well as the calcium channel selectivity of ORAI1, are crucial for its pro-apoptotic effect. Furthermore, it was observed that resistance to apoptosis in androgen-independent prostate cancer cells was associated with the down-regulation of ORAI1 expression and store-operated calcium entry. Upon ORAI1 restoration, steroid-deprived cells transfected with ORAI1 exhibited reestablished channel currents for calcium storage operations, leading to the restoration of normal apoptosis rates. Therefore, irrespective of the stimulus inducing apoptosis, ORAI1 plays a vital role in initiating apoptosis and establishing an anti-apoptotic phenotype in prostate cancer cells[87].

Concurrently, STIM1 and ORAI1 have been demonstrated to hinder cell growth by arresting human prostate cancer cells in the G_0/G_1 phase and promoting cell senescence. Additionally, STIM1 and ORAI1 inhibit the NF-κB signaling pathway and remodel the tumor microenvironment by reducing the formation of M2-type macrophages, potentially creating an unfavorable milieu for tumor growth inhibition. However, STIM1 can also promote cell migration and EMT through the activation of transforming growth factor-beta, Snail, and Wnt/β-Catenin pathways[88]. These findings collectively indicate that STIM1 and ORAI1 play a multifaceted and vital regulatory role in prostate cancer development, encompassing crucial biological processes such as cancer cell growth, apoptosis, and metastasis.

Therefore, this paper discussed prevalent cancer types globally. Table 1 below enumerates the functions and subcellular localizations of these genes during AICD[89-105]. Due to the limited availability of cancer prognosis-related information regarding AICD genes, an extensive analysis was conducted using clinical data from the database provided by the American Cancer Letters and Biology Institute (https://www.aclbi.com/static/index.html/). Table 1, establishes a comprehensive gene prognosis model centered on AICD, aiming to assess the prognostic significance of individual genes across several types of cancer.

AICD AS POTENTIAL CANCER TREATMENT

The elucidation of the AICD mechanism has offered valuable insights into prospective drug investigations, underscoring its promising potential in cancer treatment. In recent years, there has been a notable surge of interest within the scientific community towards harnessing the AICD mechanisms for cancer therapy. This intricate mechanism involves the engagement of eATP with the P2X7R located on the cell membrane's surface, culminating in heightened intracellular calcium ion levels and concurrent activation of the PI3K/Akt signaling cascade, which impacts molecules including NF-KB, toll-like receptor 4, and tumor necrosis factor-alpha (TNF-α), ultimately triggering cell death. This comprehensive exploration into the molecular intricacies furnishes a robust scientific foundation for the future development of novel therapeutics targeting this pathway.

Caffeine exerts its impact by facilitating the degradation of intracellular adenylate (AMP), thereby intensifying the cellular consumption of ATP. In the context of the rat brain, a notable interplay emerged between chronic high-intensity interval training (HIIT) and caffeine consumption, revealing a linkage to the activity of Na^+-K^+-ATPase and antioxidant enzymes within the brain, alongside the manifestation of anti-anxiety behaviors. Notably, caffeine administration was observed to amplify anxiety-related behaviors, while concurrently mitigating alterations induced by HIIT in the antioxidant system and Na^+-K^+-ATPase activity[106]. This implies that caffeine could potentially heighten AMP degradation through the modulation of ATPase activity. Notably, a mitochondrial reverse transport inhibitor, atractyloside, perturbs adenylate transport within mitochondria, thus precipitating intracellular ATP degradation.

Furthermore, recent investigations have revealed a spectrum of novel P2X7R inhibitors, including emodin, which have demonstrated substantial efficacy in suppressing P2X7R-mediated breast cancer invasion, signifying their promising potential for prospective clinical applications[64]. A notable example is brilliant blue G (BBG), a P2X7R inhibitor, crucial in addressing bone cancer pain. Noteworthy findings have indicated that BBG-mediated inhibition of P2X7R or

utilization of small interfering RNA directed against P2X7 in RVM distinctly diminishes spinal cord 5-HT levels and Fos expression[107]. Additionally, it is noteworthy that P2Y12 receptor selective antagonists play a vital role in diverse malignancies. Clopidogrel, for instance, has been identified as an efficacious selective P2Y12 receptor antagonist, pivotal in orchestrating platelet function regulation and eliciting positive effects in the context of cancer[108].

Furthermore, the dose-dependent attenuation of ATP-induced intracellular calcium concentration signaling [$(Ca^{2+})i$] through the phospholipase C inhibitor U73122 underscores its important role. These pharmacological attributes compellingly underscore the functional expression of G-protein-coupled P2Y2 receptors in esophageal squamous cell cells[109]. To encapsulate, P2 receptor-associated inhibitors confer potent suppression of tumor cell proliferation, invasion, immune modulation, angiogenesis, and tumor microenvironment regulation, as well as influencing drug targets and enhancing chemotherapy sensitization. Moreover, these inhibitors may fortify immune cell-mediated tumor assaults, thus augmenting therapeutic outcomes.

Suppression of PANX1 protein levels through shRNA-mediated downregulation or application of channel-blocking agents such as carbenoxolone and probenecid has robustly attenuated cell proliferation and migration, concurrently stimulating melanin synthesis. Intriguingly, cell surface biotin labeling analysis revealed an intracellular reservoir of PANX1 within melanoma cells. Notably, PANX1's potential modulation of signal transduction *via* the Wnt/β-catenin pathway is underscored by the significant reduction in β-catenin levels following PANX1 silencing[110]. Concurrently, berberine (BBR) exhibited notable effects on MDA-MB-231 cell viability, fostering dose-dependent lactate dehydrogenase release, while effectively curtailing colony formation and migratory potential. BBR further exhibited marked suppression of pro-inflammatory cytokine secretion, including IL-1α, IL-1β, IL-6, and TNF-α[111]. Subsequent investigations revealed downregulated expressions of P2X P2X7, NOD-like receptor family pyrin domain containing 3 (NLRP3), pre-Caspase-1, apoptosis-related speckle-like protein (ASC) encompassing caspase activation and recruitment domains, Caspase-1 p20, IL-18, and IL-1β in the NLRP3 inflammatory body pathway. Moreover, decreased mRNA levels of NLRP3, caspase-1, and ASC further corroborated these findings[111].

The concept of AICD mechanism has garnered significant interest within the realm of cancer therapy, emerging as a focal point for exploration within innovative anti-cancer therapeutic avenues. Serving as a fundamental underpinning of cell demise, the AICD mechanism is intrinsically intertwined, either directly or indirectly, with diverse modes of cell death. This interplay holds the potential to reveal intricate associations among distinct cell death modalities. Recent investigations underscore the promise of harnessing AICD as a catalyst for novel therapeutic approaches, potentially encompassing novel drug development and synergistic utilization with established treatments to enhance therapeutic efficacy. Nevertheless, while the appeal of the AICD mechanism is compelling, its practical application necessitates further comprehensive scrutiny, aimed at elucidating intricate molecular underpinnings, refining its applicability spectrum, and addressing safety parameters. Furthermore, this study made use of the ClinicalTrials.gov website (https://clinicaltrials.gov/), a comprehensive repository of clinical trial information, to compile a list of AICD-associated genes that have undergone completed clinical trials (Table 2).

REFLECTIONS ON ATP AND AICD

The intricate interplay between ATP and AICD within the tumor microenvironment, its intersection with anti-tumor immunity, and the nuanced impact of individual variances on cancer progression and therapeutic responsiveness pose an interesting challenge for scientific research. Firstly, while the pivotal role of ATP in instigating apoptotic cascades within neoplastic cells is acknowledged, the precise orchestration of its regulatory mechanisms remains unknown.

Immunological integrity serves as a robust "fortification" to the human body. However, the link between extrinsic factors and unhealthy lifestyles may affect the strength of immune cells over time, leading to gradual weakness and an eventual breach in the body's protective barrier. Consequently, the body becomes susceptible to infections and ailments. AICD has demonstrated its potential to galvanize the immune system. However, the specific recognition and response mechanisms of immune cells against antigens liberated by AICD remain shrouded in mystery. The elevated metabolic activity of tumor cells and their heightened demise in the TME lead to an augmented ATP concentration. Remarkably, ATP undergoes gradual enzymatic transformation into adenosine through the sequential CD39→Ecto-5′-Nucleotidase →androgen receptor pathway. Consequently, the dynamic distribution and concentration of ATP in the tumor microenvironment represents an unsolved conundrum that warrants closer investigation.

The notion of a specific immune response pertains to the targeted immune reaction directed against a particular pathogenic entity. Molecules intricately linked with immunological responses possess the capacity to instigate cell death, often paralleled by the demise of infected cellular hosts. However, the induction of cell death through ATP activation may yield diverse outcomes in distinct immune cell types. Heterogeneous immune cell populations exhibit varying sensitivities to ATP-triggered cell death, thereby influencing the vigor and efficiency of immune functionalities. Interventions targeting the adenosine pathway not only counteract immunosuppression but also amplify ATP accumulation within the tumor microenvironment through the CD39 blockade. Abundant ATP receptors in immune cells, including dendritic cells, macrophages, and neutrophils, foster heightened immune activity upon exposure to eATP.

Furthermore, the intricate role of ATP in modulating immunosuppressive dynamics within the tumor microenvironment remains partially veiled. Often characterized by immunosuppressive traits, the tumor microenvironment's potential for immune subversion, and whether ATP release can serve as a countermeasure to revert this suppressive state, warrant further exploration. Remarkably, individual responsiveness to ATP stimulation may exhibit substantial variation, potentially rendering certain individuals more predisposed to heightened susceptibility to AICD, while others may manifest attenuated responses. Genetic idiosyncrasies among individuals underpin a broad spectrum of cancer treatment

Table 2 Clinical trials for adenosine triphosphate induced cell death

NCT number	Conditions	Drugs	Brief summary
NCT02587819	Carcinoma, basal cell	Treatment with BSCT	This phase 1 clinical trial assesses the safety of BSCT (anti-nf-P2X7) 10% Ointment in basal cell Carcinoma patients
NCT03088644	Healthy	Drug: JNJ-54175446; Drug: 18F-JNJ-64413739	Open-label trial investigates P2X7R occupancy using PET tracer 18F-JNJ-64413739 for P2X7R with JNJ-54175446
NCT03437590	Healthy	Drug: JNJ-55308942; Drug: [18F]-JNJ-64413739	The primary objective of this investigation is to quantify the inhibition of [18F]-JNJ-64413739 uptake in the brain upon achieving peak plasma concentration (Tmax) and at 24 hours after administering a single dose of JNJ-55308942. Additionally, this study aims to establish a comprehensive model for understanding the interplay between JNJ-55308942 exposure and its receptor interactions
NCT01664000	Solid tumors	Drug: Thioureidobutyronitrile	A phase 1 open-label trial with dose escalation is being conducted to explore the safety, pharmacokinetics, and pharmacodynamics of intravenous kevetrin (thioureidobutyronitrile) in advanced solid tumor patients
NCT00899158	Pancreatic cancer	Other: Immunologic techniques; Other: Laboratory biomarker analysis; procedure: Biopsy	The study seeks to clarify how caspase-3, phosphatidylinositol-3 kinase, and 3-methylhistidine contribute to skeletal muscle wasting in weight loss among pancreatic cancer patients
NCT04972188	Healthy	ZYIL1 capsule	This phase I study investigates the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered ZYIL1 in healthy adult subjects through a prospective, open-label, multiple-dose approach
NCT04015076	Healthy	Drug: Inzomelid; Drug: Placebo	This phase 1 study aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and food effects of Inzomelid in healthy adults through a randomized, double-blind, placebo-controlled design. An open-label cohort will also verify the safety, pharmacokinetics, and pharmacodynamics of Inzomelid in adult patients with cryopyrin-associated periodic syndromes
NCT04938414	Subarachnoid hemorrhage, aneurysmal	Diagnostic test: Lumbar puncture	Caspase-1 inhibition mitigates pyroptotic neuroinflammation and alleviates cerebrospinal fluid circulation impairment post subarachnoid hemorrhage
NCT02872818	Apoptotic signal pathways in endometrial hyperplasia	Drug: 17β estradiol hemihydrate; Drug: Metformin; Drug: Medroxyprogesterone acetate	This study aims to clarify apoptotic signaling pathways involving Survivin, Bcl-2, Bax, c-Myc, and caspase-9 in a rat model of iatrogenic endometrial hyperplasia treated with metformin and medroxyprogesterone acetate
NCT02466516	Non-alcoholic steato-hepatitis	Drug: SEL; Biological: SIM	This phase 2 randomized, open-label trial evaluates the safety, tolerability, and efficacy of GS-4997 alone or combined with simtuzumab (SIM) in non-alcoholic steatohepatitis subjects with F2-F3 fibrosis stages
NCT00169130	Lymphoma, large-cell, diffuse	Drug: Doxorubicin; Drug: Cyclophosphamide; Procedure: Autologous stem cell transplantation	This prospective study investigates the ACVBP regimen followed by autologous stem cell transplantation in treatment-naive patients aged 60 or below with low-intermediate risk diffuse large B-cell lymphoma and BCL-2 overexpression
NCT02582879	Chronic Lymphocytic Leukemia (CLL)	NA	This multicenter, prospective, observational registry examines CLL/SLL patients initiating approved oral kinase inhibitors, BCL-2 inhibitors, or other anti-CLL therapies. The study aims to comprehensively analyze treatment patterns, including patient characteristics, resource use, clinical outcomes, and patient-reported outcomes
NCT02226965	Lymphoma, diffuse large B-Cell	Drug: PNT2258	A phase II trial investigates PNT2258 in patients with relapsed or refractory diffuse large B-cell lymphoma
NCT00005032	Lung cancer	Biological: Oblimersen sodium; Drug: Paclitaxel	A Phase I/II trial explores the combination of G3139, a BCL-2 antisense oligonucleotide, with paclitaxel for treating recurrent small cell lung cancer
NCT02419560	Lymphoma, mantle-cell recurrent lymphoma, mantle-cell	Drug: ABT-199 and ibrutinib combination	This study aims to determine the optimal dosing regimen for combining ibrutinib with ABT-199 to treat relapsed or refractory mantle cell lymphoma
NCT00085228	Prostate cancer	Biological: Oblimersen sodium; Drug: docetaxel	Docetaxel and similar agents block tumor cell division through diverse mechanisms, while oblimersen may boost docetaxel's impact by sensitizing tumor cells to enhance its efficacy
NCT03255096	Diffuse large B-cell lymphoma high-grade B-cell lymphoma	Drug: RO6870810; Drug: Venetoclax; Drug: Rituximab	An open-label Phase Ib study assessing the safety, pharmacokinetics, and clinical effects of RO6870810 and Venetoclax in patients with relapsed/refractory DLBCL and/or high-grade B-cell lymphoma carrying gene rearrangements (MYC and/or BCL2 and/or BCL6), with or without Rituximab
NCT00001572	B Cell lymphoma follicular lymphoma	Drug: Id-KLH Vaccine; Drug: QS-21 (Stimulation-QS-21) Drug	To evaluate new vaccine formulations for viability and adverse effects, as well as analyze immune responses targeting the patient's lymphoma-specific

	neoplasm		idiotype
NCT00062010	Lung cancer	Biological: Interferon alpha; Drug: 13-cis-retinoic acid; Drug: Paclitaxel	In patients with recurrent small cell lung cancer undergoing interferon alfa, isotretinoin, and paclitaxel treatment, the investigation aims to determine treatment response frequency and duration, evaluate regimen toxicity, assess overall survival duration, and explore potential links between bcl-2 levels in peripheral blood monocytes and treatment outcomes
NCT00039481	Cardiac toxicity; unspecified childhood solid tumor, protocol specific	Biological: Oblimersen sodium; Drug: dexrazoxane hydrochloride; Drug: Doxorubicin hydrochloride	In this phase I trial, oblimersen's effectiveness, combined with chemotherapy and dexrazoxane, is assessed for treating relapsed or refractory solid tumors in youth. Chemotherapeutic agents inhibit tumor cell division through diverse mechanisms, impeding growth or triggering cell death. Oblimersen is anticipated to heighten the potency of doxorubicin and cyclophosphamide by increasing tumor cell sensitivity. Dexrazoxane, a chemoprotective agent, may also shield normal cells from chemotherapy's adverse effects
NCT00666666	Adenocarcinoma of the prostate stage iv prostate cancer	Drug: AT-101; Drug: Bicalutamide; Other: LHRH agent	In this phase II trial, gossypol's potential to hinder tumor cell growth by blocking blood flow is studied when combined with androgen ablation therapy for newly diagnosed metastatic prostate cancer. Androgens stimulate prostate tumor cell proliferation, which can be reduced by luteinizing hormone-releasing hormone agonists and drugs such as bicalutamide. The simultaneous use of gossypol and androgen ablation therapy appears to hold potential as a viable treatment approach for prostate cancer
NCT00003103	Bladder cancer breast cancer colorectal cancer	Biological: Oblimersen sodium; Drug: Docetaxel	This phase I/II trial evaluates oblimersen's effectiveness in treating solid tumors that have not responded to previous therapies, utilizing various mechanisms to halt tumor cell division, leading to growth arrest or cell death
NCT03080311	Small cell lung cancer; solid tumor	Drug: APG-1252	In this Phase I trial, the safety, pharmacokinetic, and pharmacodynamic profiles of intravenously administered APG-1252 are examined in patients with small cell lung cancer or other solid tumors
NCT00016263	Melanoma (skin)	Biological: Oblimersen sodium; Drug: Dacarbazine	This randomized study compares Dacarbazine alone to Dacarbazine combined with G3139 (Bcl-2 Antisense Oligonucleotide) in patients with advanced malignant melanoma
NCT00169000	Metastatic breast cancer	Drug: Capecitabine; Drug: Docetaxel	Phase I study using accelerated titration design to determine MTD of capecitabine (days 1-14) combined with fixed dose docetaxel (75 mg/m2 IV, day 8). Nine patients will be treated at MTD, evaluating pharmacokinetics, Bax: Bcl-2 ratios, and antitumor response
NCT02997423	Glioblastoma		This multi-institutional, consortium-based, non-interventional study aims to assess if high cytochrome c oxidase activity in newly diagnosed primary GBM tumor specimens is linked to reduced overall survival (primary outcome) and progression-free survival (secondary outcome) times
NCT01205503	Breast cancer non-hodgkin's lymphoma	Drug: Mesna; Drug: Saline; Drug: Doxorubicin	This study aims to investigate if mesna can inhibit specific chemical alterations in the blood of doxorubicin-treated patients. Researchers hypothesize that these changes may be associated with "chemobrain," a cognitive impairment reported by some chemotherapy recipients
NCT01037790	Adult solid tumor adenocarcinoma of the colon adenocarcinoma of the rectum	Drug: PD-0332991	PD 0332991 has the potential to hinder tumor cell growth by blocking key enzymes vital for cell proliferation. This phase II trial evaluates PD 0332991's effectiveness and side effects in treating patients with resistant solid tumors
NCT02154490	Recurrent squamous cell lung carcinoma stage iv squamous cell lung carcinoma AJCC v7	Drug: Docetaxel; biological: Durvalumab; Drug: Erlotinib hydrochloride	Create a National Clinical Trials Network for screening sizable yet homogeneous cancer populations, assigning them to a multi-sub-study "Master Protocol." Assess the screen success rate, defined as the percentage of screened patients enrolling in a therapeutic sub-study

outcomes and their efficacy. The profound impact of individual variations in ATP responsiveness on cancer progression and therapeutic response underscores a pressing inquiry, necessitating thorough investigation into the underpinning mechanisms and conceivable implications.

Additionally, the intricate interplay between the complex and diversified tumor microenvironment and individualized patterns of ATP responsiveness can engender pronounced dissimilarities in cell death incidence and severity. Such variances may closely interlink with the tempo of tumor evolution, aggressiveness, and treatment susceptibility. Nonetheless, a comprehensive resolution to this enigma remains elusive, with further research needed to unravel the intricate relationships between ATP responsiveness, individual differences, and the multifaceted intricacies of the tumor microenvironment.

LIMITATIONS AND FUTURE

ATP, an essential extracellular signaling molecule, has been recognized as a cause of cell death induced by high eATP concentrations. It can trigger cell death through diverse mechanisms and directly impact tumor cells to inhibit their

proliferation, invasion, and metastasis. Additionally, ATP can hinder tumor development by activating the immune system. However, the precise mechanisms and occurrence of AICD have been the subject of debate and remain unclear until now, despite preliminary insights into the relationship between AICD and cancer having been gained. Further investigation is warranted to elucidate the intricate mechanisms underlying AICD, particularly at the cellular and molecular levels There also needs to be a comprehensive characterization of the distinctive changes associated with this process. Additionally, a comprehensive understanding of the interplay and relative significance of AICD in relation to other cell death pathways in diverse disease contexts is crucial. Moreover, investigating the varied responses of different cell types to AICD and exploring potential cell-specific mechanisms are important avenues for future research. These endeavors will enhance our understanding of the molecular mechanisms governing AICD, facilitate the identification of novel regulators, and offer new targets and strategies for the development of cancer therapies and other related diseases.

The introduction of the concept of AICD has sparked increasing interest among researchers regarding its association with tumors. Investigations into this relationship have encompassed numerous prevalent cancer types, examining the correlation between AICD and various tumor characteristics. However, due to insufficient biological evidence and experimental verification, these studies have offered indirect evidence of the connection between AICD and cancer. The precise role of genes in the direct or indirect interplay between AICD and tumors remains unclear. Consequently, these studies have been unable to identify the genes and features that may exert a more significant influence on the relationship between AICD and cancer. Consequently, further research is imperative to comprehensively explore and validate the intricate association between AICD and cancer, ultimately identifying the pivotal factors involved in this interplay.

Moving forward, it is crucial to validate the potential of AICD in clinical applications and advance the development of therapeutic strategies that induce AICD with high efficiency and selectivity. Additionally, synergistic combinations with immunotherapy should be further explored. In summary, AICD represents an autonomous and innovative cell death paradigm. However, comprehensive investigations are needed to elucidate the precise mechanisms underlying AICD and establish the intricate connections between AICD and cancer.

CONCLUSION

ATP serves as a vital extracellular signaling molecule for cell survival, yet excessive ATP can induce cell death. With the introduction of the concept of AICD, extensive literature has emerged focusing on its investigation and elucidation. Researchers have made discoveries regarding ATP-activated proteins and provided comprehensive reviews on the topic. However, a comprehensive synthesis of the literature remains lacking, especially an overview of the mechanisms underlying AICD. Further investigation is needed to explore the intricate details of AICD, particularly in terms of its cross-regulation and mutual influence with other cell death pathways, as well as its relative importance in various disease conditions. Moreover, the distinctive changes occurring at the cellular and molecular levels during AICD have yet to be fully described.

This paper provides an in-depth exploration of the multifaceted mechanisms through which AICD. It delineates how ATP serves as a mediator of apoptosis *via* diverse pathways, encompassing the activation of caspases within the cysteine protease family, the regulation of mitochondrial membrane potential, and the modulation of apoptosis-related protein expression. Additionally, ATP exerts a profound impact on cancer cells by instigating various forms of cell necrosis, including necrotic apoptosis and necrotic tumor cell death. The involvement of ATP in orchestrating the delicate balance between cell survival and death is underscored through its regulation of the autophagy process.

In the realm of cancer biology, ATP emerges as a pivotal regulator influencing tumor cell proliferation, invasion, and metastasis. The article underscores ATP's role in impeding tumor growth by activating apoptosis pathways and enhancing immune-mediated tumor clearance through the induction of tumor cell necrosis. Furthermore, ATP's contribution extends to the modulation of the tumor microenvironment, influencing factors such as inflammation and immune responses, thereby exerting a significant impact on tumor development.

On the therapeutic front, the study accentuates the potential of ATP as a therapeutic agent for inducing cell death. By precisely adjusting ATP levels and subsequently activating core pathways involved in cell death, targeted induction of tumor cell death becomes achievable, offering promising prospects for therapeutic intervention. This comprehensive exploration establishes a crucial theoretical foundation for future research endeavors and clinical applications.

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FOOTNOTES

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Lok B collected and collated the data and produced a visual atlas; Sandai D presents the conceptualization and methodology, revises manuscripts, conducts reviews and edits, and is responsible for project management; Zhang HL presented the conceptualization and methodology, analyzed the data, and wrote the first draft; Zhang ZW, Song ZJ, Babu D, Tabana Y, Dahham SS, Adam Ahmed Adam M, Wang Y, and Wang W presented the conceptualization and methodology, analyzed the data, and conducted the review and editing; Zhang HL, Zhao R, Barakat K, Harun MSR, Shapudin SNM and Lok B collected and collated the data and produced a visual atlas; Sandai D presents the conceptualization and methodology, revises manuscripts, conducts reviews and edits, and is responsible for project management; both Sandai D and Song ZJ give detailed guidance to this paper, which is of great significance. Therefore, as a co-corresponding author; all authors have read and approve the final manuscript.

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REVIEW

Update on current diagnosis and management of anaplastic thyroid carcinoma

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Abstract

Well-differentiated thyroid carcinoma has a favorable prognosis with a 5-year survival rate of over 95%. However, the undifferentiated or anaplastic type accounting for < 0.2%, usually in elderly individuals, exhibits a dismal prognosis with rapid growth and disappointing outcomes. It is the most aggressive form of thyroid carcinoma, with a median survival of 5 mo and poor quality of life (airway obstruction, dysphagia, hoarseness, persistent pain). Early diagnosis and staging are crucial. Diagnostic tools include biopsy (fine needle aspiration, core needle, open surgery), high-resolution ultrasound, computed tomography, magnetic resonance imaging, [(18)F]fluoro-D-glucose positron emission tomography/computed tomography, liquid biopsy and microRNAs. The *BRAF* gene (*BRAF-V600E* and *BRAF* wild type) is the most often found molecular factor. Others include the genes *RET, KRAS, HRAS,* and *NRAS*. Recent management policy is based on surgery, even debulking, chemotherapy (cisplatin or doxorubicin), radiotherapy (adjuvant or definitive), targeted biological agents and immunotherapy. The last two options constitute novel hopeful management modalities improving the overall survival in these otherwise condemned patients. Anti-programmed death-ligand 1 antibody immunotherapy, stem cell targeted therapies, nanotechnology achievements and artificial intelligence implementation provide novel promising alternatives. Genetic mutations determine molecular pathways, thus indicating novel treatment strategies such as anti-BRAF, anti-vascular endothelial growth factor-A, and anti-epidermal growth factor receptor. Treatment with the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib has been approved by the Food and Drug Administration in cases with *BRAF-V600E* gene mutations and is currently the standard care. This neoadjuvant treatment followed by surgery ensures a two-year overall survival of 80%. Prognostic factors for improved outcomes have been found to be younger age, earlier tumor stage and radiation therapy. A multidisciplinary approach is necessary, and the therapeutic plan should be individu-

alized based on surveillance and epidemiology end results.

Key Words: Thyroid diseases; Thyroid cancers; Anaplastic carcinoma; Undifferentiated carcinoma; Neck mass; Aggressive malignancies

Core Tip: Anaplastic thyroid carcinoma is uncommon but one of the most lethal neoplasms. The optimal management remains unclear. The addition of novel targeted therapy and immunotherapy to the traditional management of surgery, radiation and chemotherapy has improved the outcomes. Multimodality management and the emerging use of individualized treatment based on novel therapeutic agents offers promising results. However, further research efforts involving the molecular microenvironment and biological drivers should be made.

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INTRODUCTION

Thyroid carcinoma incidence is increasing, but that of the anaplastic and medullary types remains rather stable. The overall increase is due mainly to the rise of the most commonly occurring papillary carcinoma, which is associated with the best prognosis[1-3]. The incidence of anaplastic carcinoma in Europe has been assessed to be far less than 6 cases per 100000 population, more precisely, 0.1-0.3 cases per 100000 population in Denmark, the Netherlands and Wales[2,4,5] and 0.12-0.2 cases per 100000 population in the United States[3]; thus, it has been characterized as a rare disease[6].

The 5-year survival of a well-differentiated thyroid carcinoma exceeds 95%[7]. In contrast, the undifferentiated form, also called by a revised and better term, anaplastic carcinoma determined from World Health Organization classification [8], accounts for less than 0.2%[9] or as much as 1%-2% of all thyroid malignancies[10,11]. It comes from the follicular epithelium and constitutes one of the most lethal neoplasms related to disappointing outcomes[4,9,11]. Its median survival is restricted to only 4 to 6 mo, accompanied by poor quality of life[4,10].

Rapidly growing neck tumors are often accompanied by devastating and occasionally life-threatening events. They may invade the trachea, causing airway obstruction and asphyxia; the esophagus, causing dysphagia; the recurrent laryngeal nerve, causing paralysis and hoarseness; major vessels, causing manifestations of superior vena cava syndrome or brain intermittent ischemia; and neural plexuses, causing persistent pain. Additionally, at the time of diagnosis, metastases are found in half of cases, mainly pulmonary metastases (40%), followed by brain metastases (10%)[4,9,12-14].

A long existing untreated nodular goiter (30% of cases) or known history of papillary carcinoma is usually found mainly in the elderly with female predominance[3,4]. Preexisting papillary carcinoma may indicate a potent divergent transformation[15,16]. Early diagnosis based mainly on ultrasound (US) and core needle biopsy is crucial[17-21]. The following staging after the initial diagnosis of anaplastic carcinoma is of great importance and can be achieved by computed tomography (CT), magnetic resonance imaging (MRI)[18,19], and preferably positron emission tomography/CT (PET-CT)[17,22,23]. Modern molecular testing by revealing implicated genes, basically the *BRAF* gene (*BRAF-V600E* and *BRAF* wild type), and other molecules[24-27] can contribute to more accurate diagnosis but most importantly determine molecular pathways indicating novel treatment strategies by targeted biological factors, *i.e.,* anti-BRAF, anti-vascular endothelial growth factor (VEGF)-A or anti-epidermal growth factor receptor (EGFR) agents[24].

Nanotechnology achievements may offer either a vehicle for advanced drug delivery systems promoting targeted therapy[28,29] or a core for chemo-photothermal (lenvatinib-laser irradiation) therapy[30]. Additionally, these advances may provide tools for diagnosing disease progression in the form of magnetic or radiolabeled probes[29]. Immunotherapy with an anti-programmed cell death-ligand 1 (PD-L1) monoclonal antibody (atezolizumab) may increase the action of radiotherapy on cancer cells and is a novel innovation[31]. Stem cell-targeted therapies are other novel emerging alternatives with promising perspectives[24,32,33].

Machine learning with deep learning along with artificial intelligence implementation has provided preliminary encouraging results for diagnosis, imaging assessment, treatment and outcome prediction. It now remains to be used in clinical practice[10,34]. A multidisciplinary approach must be followed with an individualized therapeutic plan based on surveillance and epidemiology end results (SEER)[3,9,35-37].

The management policy constitutes the standard treatment, including surgery first of all, even debulking surgery, adjuvant chemotherapy that mainly uses cisplatin or doxorubicin and docetaxel-paclitaxel, and accelerated hyperfunctional external beam radiotherapy, preferably neo-adjuvant and definitive. It can increase the median survival up to 10 mo[24]. The novel hopeful management by targeted biological agents and immunotherapy has further improved the overall survival in these otherwise condemned patients[4,9,24,38,39].

Treatment with the combination of the *BRAF* inhibitor dabrafenib and the *MEK* inhibitor trametinib was approved by the Food and Drug Administration (FDA) of the United States in 2014 for mutated melanoma and in 2018 for mutated anaplastic thyroid carcinoma; thus, it has already been used successfully in cases of metastatic or locally advanced inoperable anaplastic thyroid carcinoma with *BRAF-V600E* gene mutation. This targeted therapy has been recommended as neoadjuvant treatment followed by surgery. It constitutes the standard care and ensures a two-year overall survival of 80%[4,24,40,41].

The main prognostic factors for improved outcomes have been younger age, earlier tumor stage, tumor size, multifocality, radiation therapy and novel targeted therapy[10,42]. This narrative review evaluates the current knowledge on anaplastic thyroid carcinoma with extreme aggressiveness and a dismal prognosis, emphasizing proper diagnosis and management. This study was based on the data of an extensive literature review from PubMed extending to September 2023, focusing particularly on full-text papers published only in the English language over the last five years.

DIAGNOSIS

The diagnostic steps are shown schematically in Figure 1.

Presentation

The anaplastic thyroid carcinoma exhibits a rapid onset with a large, hard, painful neck mass, cough with or without hemoptysis and dyspnea (35%) in cases of trachea invasion, hoarseness (40%) or dysphagia (40%), with local spread in over 50% of cases, lymph node involvement, possible skin invasion, and rapid evolution with dramatic invasion of adjacent structures that may need urgent intervention as mentioned above in the introduction section[4,6,43].

A recent large study from the United States including 5359 patients with anaplastic thyroid carcinoma provides an analysis of several presentation characteristics. The majority of patients were women (58%), non-Hispanic white (80%), with a median age of 70 ± 12 years, a median tumor size of 6.1 cm (range 4.5-8 cm), and distant metastases (29%)[44].

It is important for rapidly growing neck swelling to differentiate anaplastic thyroid carcinoma from thyroid lymphoma by biopsy[45] since they have completely different management strategies. The lymphoma requires no surgical intervention but only R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine or otherwise called oncovin, and prednisolone) accompanied by immediate extreme volume reduction and long-term excellent outcomes[46].

Imaging

US can be used to detect heterogeneous echogenicity, abnormal shape, calcifications, increased vascularity, diffuse infiltration of adjacent tissues and regional lymph node involvement. US plain or preferably high resolution is the first step of exploration[18,19], followed preferably by core needle biopsy[21]. After establishing the diagnosis of the primary tumor of anaplastic thyroid carcinoma, staging imaging is necessary for local tumor extension assessment and revealing distant metastases.

Contrast-enhanced CT or MRI and magnetic resonance angiography can reveal any involvement of major vessels or lymph nodes and any other local involvement or distant metastases. CT can be used to detect heterogeneous tumor appearance, necrosis, calcifications, hypervascularity, and possible infiltration of the trachea and esophagus. CT is preferred over MRI[18,19]. Additionally, fiberoptic laryngoscopy for vocal cord evaluation, bronchoscopy and esophagoscopy are necessary prerequisites[20,43].

However, more precise assessment has been offered by [(18)F]fluoro-D-glucose PET-CT, which ensures better anatomic location with active metabolic uptake detecting occult deposits[17,23,47]. It can be especially valuable in elderly patients for accurate disease setting assessment that can precisely determine the appropriate management strategy[22].

Molecular testing for implicated genes and other molecules

Prompt diagnosis and on-time management without any delay are imperative tasks, particularly in severe life-threatening complications. Molecular testing is indicated to better determine mutations and proper targeted therapy either as neo-adjuvant in unresectable cases or adjuvant after surgical excision[48], especially in cases of refractory carcinoma[49]. The American Thyroid Association (ATA) recent guidelines include recommendations for molecular testing for anaplastic thyroid carcinoma[50].

The *BRAF* gene mutation (*BRAF-V600E* and *BRAF* wild type) is the most important molecular factor found in 40%-50% of patients with anaplastic thyroid carcinoma[4,6,51]. The *MEK* gene has a close connection to the *BRAF* gene. Both are responsible for mitogen-activated protein kinase that promotes cell proliferation, tumor growth and angiogenesis[41,52,53]. Other mutations found involve the following genes: p53 in 63% of cases, *RET*, *RAS* (*KRAS*, *HRAS*, *NRAS*) in 22% of cases, *TERT* promoter in 75% of cases, *PIK3CA* in 18% of cases, *EIF1AX* in 14% of cases, *PTEN* in 14% of cases[6,24,50], and *NESTIN*, *CCND1*, *POU5F1*, *MCL1*, *MYBL2*, *MCL1*, *IQGAP1*, *SOX2*, and *NANOG*[33]. Additionally, epigenetic-related genes, *i.e.*, the chromatin remodeling SWI/SNF complex in 36% of cases, histone methyltransferases in 24% of cases, and DNA mismatch repair pathway genes in 10%-15% of cases, were found[6]. Gong *et al*[54] recognized 10 hub genes for anaplastic thyroid carcinoma: *CXCL8*, *CDH1*, *AURKA*, *CCNA2*, *FN1*, *CDK1*, *ITGAM*, *CDC20*, *MMP9*, and *KIF11*. *RAS* gene mutations have been reported to correlate with increased aggressiveness and increased mortality[55]. Unfortunately, targeted therapy is not yet available[50]. A positive result for mutated neurotrophic tyrosine receptor kinase (*NTRK*) gene testing is valuable to select patients for therapy by tropomyosin receptor kinase inhibitors (larotrectinib, entrectinib)[56]. miRNA-506 downregulation has been found in anaplastic thyroid carcinoma. This molecule normally regulates the WNT and NOTCH signaling pathways to adjust cell proliferation and migration. Thus, in practical view, as a new therapeutic

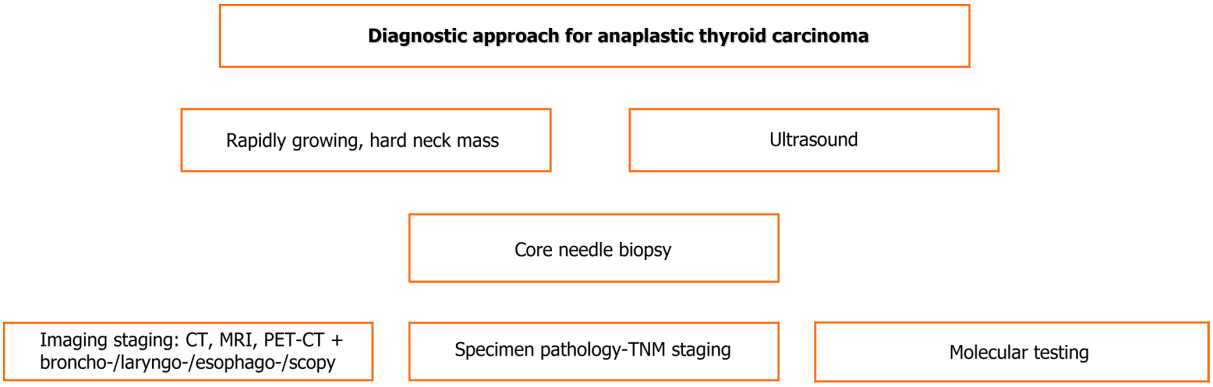

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Figure 1 Scheme of diagnostic steps for anaplastic thyroid carcinoma. CT: Computed tomography; MRI: Magnetic resonance imaging; PET-CT: Positron emission tomography/computed tomography; TNM: Tumor-node-metastasis.

targeted biological agent, it could suppress tumor progression and dissemination[25].

In an experimental model, intercellular adhesion molecule-1 (ICAM1) was an attractive target for anaplastic and papillary thyroid carcinoma by a monoclonal antibody; its distribution was explored by MRI[57]. Another molecule, collagen triple helix repeat containing-1 (CTHRC1), has been found to decrease the survival of patients with anaplastic thyroid carcinoma by promoting its progression and invasion *via* the WNT pathway and epithelial-mesenchymal transition. Blocking its action could be particularly useful[58]. Histone lysine lactylation represents a novel epigenetic mark that can boost the proliferation of anaplastic thyroid carcinoma. Blocking this protein may increase the action of *BRAF-V600E* gene inhibitors, thus preventing the progression of the mutated malignancy[51]. PD-L1 expression was found to be positive in a high proportion in papillary 87% but with weaker and patchy expression, and in anaplastic thyroid carcinoma 73%, indicating that the latter can exhibit a better response to immunotherapy[59].

Biopsy

It is obvious, that in cases of rapidly enlarging neck nodules, the necessary first step is an US imaging performance. Advances in the US technology provide precise diagnostic capability by high resolution US. However, then biopsy is fundamental to make the diagnosis. Fine needle aspiration (FNA) cytology using a 21-25 gauge needle under US guidance has been widely used as an initial step in diagnosis by cytologic examination[20,21,34,45,60]. However, due to its high false-negative results, low sensitivity of 54%-61% *vs* 77%-80% of core needle biopsy (CNB), and specificity of 87% *vs* 100% of CNB[20,21] or often inconclusive results, this option tends to be omitted recently in favor of CNB. Because of performance, using it is considered a vain spending of time[21,45].

CNB is performed under US guidance and by local anesthesia using a 16-20 Ga needle to take at least 2-3 tissue samples by separate punctures for histopathologic examination[20,21,45]. In addition, the sample can be immediately used for molecular testing[20]. CNB yields the most accurate diagnostic ability and thus constitutes the method of first choice instead of its application after nondiagnostic FNA, which, in contrast to current guidelines, is advised. There was no patient discomfort or malignant cell seeding or notable complications. A little bleeding requiring simple compression or hematoma formation may occur rarely[20,21,45].

Incision biopsy or open surgery biopsy under local or even general anesthesia and skin incision takes 2-3 cm^3 of tissue, avoiding any necrotic area. However, it has been abandoned and substituted by CNB[21]. Liquid biopsy is a new noninvasive genotyping diagnostic method that can detect malignant cells in serum and tumor DNA or other extracellular parts, providing valuable information. It may contribute to diagnosis, prognosis, and follow-up for assessment of the response to treatment or relapse[26,27]. All the abovementioned diagnostic tools are shown in Table 1.

Pathological staging

By definition, all anaplastic thyroid carcinomas are considered advanced and classified in stage IV by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) according to the tumor-node-metastasis (TNM) system (tumor size and local extension, regional lymph node status and distant metastases). The 8th edition of TNM classification and staging by the AJCC and UICC are shown in Tables 2 and 3[6,8,61].

MANAGEMENT

There have been several management options, including novel targeted therapy and immunotherapy[4,6,24,44,62]. They are presented below. In a recent cohort study including 97 patients, these options were presented in combination as follows: (1) Surgical intervention in 45% of cases; (2) Chemotherapy in 41% of cases; (3) Neoadjuvant or definitive radiotherapy in 35% of cases; and (4) Targeted therapy in 29% of cases. The median overall survival was 6.5 mo, and it was inferior in those who did not undergo surgery. Multivariate analysis showed that stage IVC and lack of radiotherapy

Table 1 Used diagnostic tools for anaplastic thyroid carcinoma

n	Modality
1	Plain ultrasound or preferably high resolution ultrasound
2	Core needle biopsy under ultrasound guidance preferably
3	FNA cytology under ultrasound guidance
4	Staging imaging (CT, MRI-MRA, ^{18}F-FDG PET-CT)
5	Bronchoscopy
6	Esophagoscopy
8	Fiberoptic laryngoscopy
9	Molecular testing (*BRAF, MEK, NTRK, RET, RAS, p53* genes)
10	MicroRNAs
11	PD-L1 expression
12	Liquid biopsy
13	Histopathology
14	Pathological TNM staging

FNA: Fine-needle aspiration; CT: Computed tomography; MRI-MRA: Magnetic resonance imaging/magnetic resonance angiography; ^{18}F-FDG PET-CT: [(18)F]fluoro-D-glucose positron emission tomography/computed tomography; PD-L1: Programmed death-ligand 1; TNM: Tumor-node-metastasis.

Table 2 T classification in tumor-node-metastasis system for anaplastic thyroid carcinoma of American Joint Committee on Cancer and Union for International Cancer Control 8th edition

T	Size	Extension
T1	≤ 2 cm	Limited into thyroid
T1a	≤ 1 cm	Limited into thyroid
T1b	> 1 cm and ≤ 2 cm	Limited into thyroid
T2	> 2 cm and ≤ 4 cm	Limited into thyroid
T3	> 4 cm	Limited into thyroid or extrathyroid macroscopic invasion only of thyroid muscles and subcutaneous tissue
T3a	> 4 cm	Limited into thyroid
T3b	Any size	Extrathyroid macroscopic invasion only of thyroid muscles and subcutaneous tissue
T4	Any size	Macroscopic invasion of major adjacent structures
T4a	Any size	Macroscopic invasion of larynx, trachea, esophagus, recurrent laryngeal nerve
T4b	Any size	Macroscopic invasion of carotid artery, major vessels in mediastinum, prever-tebral fascia

were associated with worse overall survival[42].

This multimodality management, including additional tyrosine kinase inhibitors, could provide a survival of more than one year[63]. Given that in 433 studied patients with advanced metastatic anaplastic thyroid carcinoma (stage IVC), there was a median overall survival of 2 mo and a one-year overall survival of 6.9%[64], better multimodality management including novel therapeutic agents is needed, especially for this most lethal form[65]. The optimal combination of multimodality treatment[63,66] and mainly the new tyrosine kinase inhibitor lenvatinib yields encouraging results[11].

Surgery

Surgery constitutes the cornerstone of treatment despite the existing debate. It may range from palliative debulking intervention to more radical resections, including total or near total thyroidectomy and extended lymphadenectomy, including the central and lateral lymph node level either unilaterally or bilaterally[6,8,36,53,61]. The above curative surgery may be performed in some patients with earlier disease and may provide, accompanied by adjuvant chemotherapy, occasional long survival over 5 years[18,19]. By multivariate analysis in a systematic review and meta-analysis, surgery and radiotherapy were found to be independent factors predicting increased overall survival[36]. Complete surgical excision followed by adjuvant therapy is the optimal opportunity for cure[4,47]. However, in general,

Table 3 Tumor-node-metastasis staging for anaplastic thyroid carcinoma of American Joint Committee on Cancer and Union for International Cancer Control 8th editiona

Stage	IVA	IVB	IVC
Parameters	T1-T3a, N0, M0	T1-T3a, N1, M0	Any T, any N, M1
		T3b, any N, M0	
		T4, any N, M0	

T: Tumor size; N0: Negative regional lymph nodes; N1: Positive regional lymph nodes; M0: Without any distant metastases; M1: Presence of distant metastases.

extreme radical resection, such as laryngectomy, tracheal resection, esophagectomy or complete neck dissection without notable oncological contribution, is not indicated[47]. Tumor removal increases the benefits of the treatment. In combination with radiation, new chemotherapy and novel gene targeted therapy can achieve locoregional disease control and improve survival and quality of life[36,41,53,65,67]. The guidelines of the National Comprehensive Cancer Network and ATA recommend surgical resection by lobectomy or near total thyroidectomy with wide lymphadenectomy in stage IVA and IVB, even in stage IVC when an R0 or at least R1 intervention could be achieved in locally resectable tumors[36,43,68-70]. However, many locally unresectable cases may respond to neoadjuvant external beam radiation, chemotherapy or even targeted therapy (dabrafenib and trametinib) for *BRAF* gene mutation, thus becoming resectable and ensuring surgical excision[43]. Timely detection and proper treatment reduce the number of advanced cases with distant metastases[9].

As shown in Figures 2 and 3, the current best practice for respectable tumors is surgery with adjuvant chemotherapy, radiation therapy and targeted therapy-immunotherapy such as dabrafenib and trametinib but immunotherapy if *BRAF* and *MET* gene mutations exist; for unresectable tumors, current best practice involves palliative surgery and targeted therapy-immunotherapy in combination with chemoradiation therapy[47].

Patients with inoperable disease may undergo palliative surgery to improve morbidity and avoid complications and life-threatening urgent events[48,71]. Unless there is debulking surgery for decompression, it includes the performance of tracheostomy and gastrostomy, preferably percutaneous by endoscopy assistance for feeding in case prior to radiation, which may cause esophageal stricture[36,48]. In cases of esophageal invasion or stenosis, feeding tube placement by an interventional radiologist can ensure enteral feeding[43].

Palliative airway management for symptom relief must be based on multidisciplinary team collaboration by designing the plan carefully. It is well known that tracheostomy may be related to morbidity and problems affecting quality of life [43]. It should be emphasized overall that patients undergoing extended surgical intervention and receiving adjuvant radiation and chemotherapy gain the chance of the best overall survival[9,48]. Aggressive locoregional surgery and radiotherapy must be performed whenever possible, and adding chemotherapy can lead to further improvement; however, in unresectable cases, radiotherapy and chemotherapy must be preferred[9].

Chemotherapy

Taxanes (paclitaxel, docetaxel, and cabazitaxel) can be effectively used to treat various forms of cancer by replicating inhibition. Doxorubicin (adriamycin) is an anthracyclin that inhibits cancer cell growth by topoisomerase II activation in the process of DNA repair. Platinum-based chemotherapy (cisplatin, carboplatin, oxaliplatin) is widely used. Attachment to DNA causes destruction of cancer cells by replicating inhibition. These chemotherapeutic drugs have been used in various cancers, including anaplastic thyroid carcinoma[6,53,67].

The ATA guidelines recommend adjuvant or neoadjuvant chemotherapy by combination of: (1) Paclitaxel with carboplatin; (2) Doxorubicin with cisplatin; (3) Doxorubicin with docetaxel; or (4) Paclitaxel alone or doxorubicin alone [6]. Unfortunately, chemoresistance often occurs in anaplastic thyroid carcinoma even in the most effective regimen of paclitaxel[6,72]. Adjuvant chemotherapy increases the median survival and the survival rate[48,67].

Subsequently, other drugs enhancing chemotherapy efficiency have been added. The combination with targeted biological agents such as dabrafenib and trametinib, in cases of mutated *BRAF* and *MEK* genes, respectively, may overcome this resistance[6,12,72]. In unmutated cases, novel immunotherapy (anti-PD-1 and anti-PD-L1) has been a recent revolution[6,12,72].

Chemotherapy added to radiation therapy further improves survival compared to radiation alone in resected cases as well as in unresected cases[73]. A randomized controlled phase II trial from 34 centers in the United States including 89 patients showed that the combination of paclitaxel chemotherapy with pazopanib, a multitargeted inhibitor of tyrosine kinase receptors and radiation therapy, was feasible, safe and promising[74].

Anlotinib, another new multitargeted inhibitor of tyrosine kinase receptors [VEGF, FGFR, platelet-derived growth factor receptor (PDGFR), c-kit] approved by the United States FDA, in combination with chemotherapy with paclitaxel, capecitabine or paclitaxel, capecitabine, and carboplatin as first-line therapy is a safe and effective treatment for locally advanced or metastatic thyroid carcinoma. As reported, it had an objective response rate of 60%, a disease control rate of 88%, and provided a progression-free survival of 25.1 wk and a median disease specification survival of 96 wk[75,76].

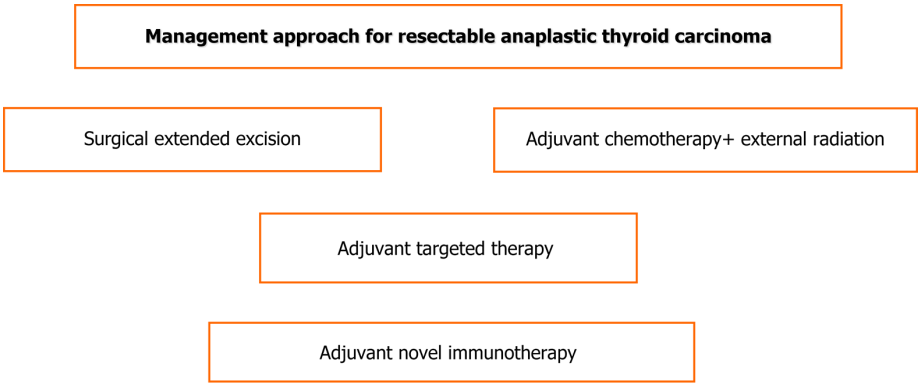

Figure 2 Scheme of treatment steps for resectable anaplastic thyroid carcinoma.

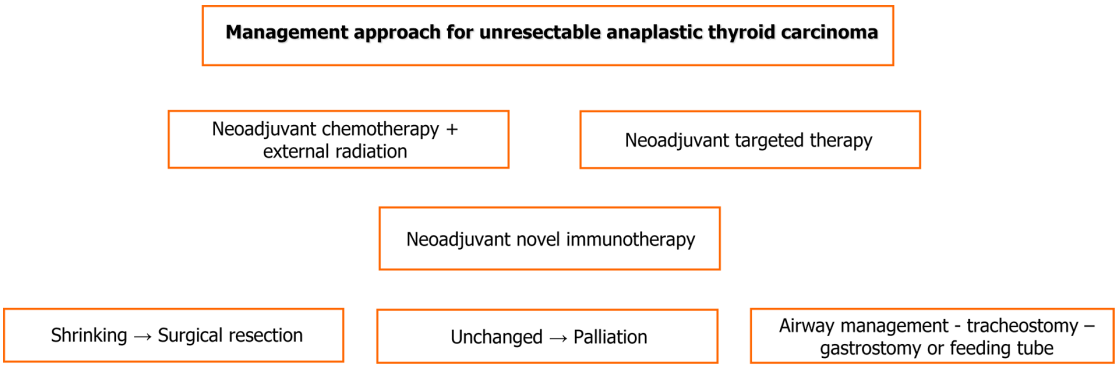

Figure 3 Scheme of treatment steps for unresectable anaplastic thyroid carcinoma.

Radiotherapy

Local rapid progression of anaplastic thyroid carcinoma and recurrence are related to the extreme malignancy of the disease. Subsequently, local control is of great importance. Radiation therapy is the main stem of every potent successful management, providing cessation of progression and regression of the tumor extent before surgery as well as prevention of recurrence after attempted surgical resection[6].

Radiotherapy can be applied as a neoadjuvant or definitive adjuvant modality generally by external beam radiation therapy (EBRT), which accelerates hyperfunction and improves median overall survival[24,48,77]. It is a necessary part of the current multimodality treatment combined with surgery, chemotherapy, targeted therapy and novel immunotherapy [9,42,63,73,74].

EBRT was assessed by a multivariate analysis in 433 stage IVC patients with anaplastic thyroid carcinoma as an independent prognostic factor of survival along with surgery and chemotherapy[24]. The optimal dose of hyperfunction EBRT varies between 45-70 G, and a subsequent hypofunction dose > 5 G can prevent local recurrence and death[6]. A retrospective study including 491 patients with anaplastic thyroid carcinoma found that the combination of radiation therapy and chemotherapy provided better overall survival than radiotherapy alone regardless of surgery and distant metastases. Prognostic factors for survival were older age, single marital status, local extension, distal metastases and surgery[73]. Among various management modalities, adjuvant chemoradiation after surgical intervention seems to be the better modality for prolonged survival in stage IVA resectable tumors without negative prognostic factors[67]. Radiotherapy may have synergy with immunotherapy by modulating microenvironmental immunity[62]. Brain metastases account for up to 10% of metastatic cases, with an overall survival of 3 mo[13]. Radiation therapy and lenvatinib targeted therapy have been reported in such cases, but with limited efficacy[14].

Targeted therapies

Targeted therapy by biological agents is based on monoclonal antibodies and is intended to block certain cancer development pathways[56,78-81]. The drugs for mechanisms of some implicated gene mutations include the following: (1) Angiogenesis-lenvatinib, sorafenib, sunitinib, vandetanib, combretastatin; (2) EGFR-docetaxel, gefitinib; (3) BRAF-dabrafenib, vemurafenib, encorafenib; and (4) MEK-trametinib, cobimetinib, binimetinib[24]. The combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib is the most widely used because it is considered more effective than each drug alone[6,24,41,82,83]. Combretastatin targets tumor vascularity. It has been used as adjuvant treatment in combination with paclitaxel - carboplatin but without notable results. Likewise, sorafenib had limited

usefulness; instead, other anti-angiogenetic agents, such as vandetanib, sunitinib, and lenvatinib, exhibited significant anti-neoplastic efficacy[24]. Vandetanib, a multitarget tyrosine inhibitor that acts mainly against EGFR and VEGF receptor (VEGFR), promotes apoptosis (programmed cell death) and inhibits tumor growth, migration and invasion[62,84]. Sunitinib, another multitarget tyrosine inhibitor, acts mainly against VEGFR and PDGFR to inhibit tumor growth by deprivation of its blood supply[62]. Lenvatinib is an inhibitor of kinase that inactivates VEGFRs (VEGFR 1, VEGFR 2, and VEGFR 3) and subsequently prevents angiogenesis and tumor growth. It has been used in anaplastic and well-differentiated thyroid carcinoma as an alternative to radioactive iodine, in inoperable hepatocellular carcinoma, and in advanced renal cell carcinoma in combination with everolimus[11,30,85]. Carfilzomib, a proteasome inhibitor approved by the United States FDA for multiple myeloma, is the most effective such drug for treating anaplastic thyroid carcinoma; by acting on cell proliferation and *p27* gene overexpression, which promotes apoptosis and cell death[62]. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor approved by the United States FDA for skin T-cell lymphoma, causes *p21* gene overexpression that promotes apoptosis and cell death[62].

A recent study from Japan including 36 patients with unresectable anaplastic thyroid carcinoma treated initially with lenvatinib showed an average survival of 5.8 mo, longer than the 2-mo survival from paclitaxel initial treatment, a response rate of 33% and a median overall survival of 5 mo[86].

Glutamin metabolism and subsequent glutaminolysis are biological features that are highly increased in anaplastic thyroid carcinoma and modulate cancer cell survival by sustaining mitochondrial function and oxygen balance. Glutaminolysis inhibition causes cell death. The tyrosine kinase inhibitors lenvatinib and sorafenib affect this signaling pathway of oncogenesis and enhance the efficiency of conventional chemotherapy, such as doxorubicin or taxanes, which otherwise may have minimal influence on patient survival[12]. ICAM1 is an interesting target of monoclonal antibodies with promising results[57]. The polo-like kinase 4 inhibitor has anticancer efficacy and synergy with sorafenib[87]. CTHRC1 promotes the progression of anaplastic thyroid carcinoma and is associated with worse outcomes[58]. The depletion of fibronectin may overcome resistance to *BRAF* gene inhibitor treatment. It can be targeted by MARK (ERK) pathway inhibition (ipilimumab, vemurafenib)[88]. Additionally, diclofenac added to *BRAF* gene inhibitors by targeting metabolism overcomes any resistance and maximizes the treatment effect[89]. Targeting the EZH2 complex promotes anticancer activity and can be a promising strategy[90]. Recent research data showed that one-carbon metabolism had a possible role in metabolic stress, and its targeting would be a valuable promising therapy[12].

Immunotherapy

Immunotherapy has been applied increasingly on a preliminary experimental basis but with promising future perspectives. Thus, it has been included in many research protocols. The existing immunotherapy regimens in combination with targeted therapy (dabrafenib - trametinib) can provide a further potential increase in effectiveness and improved survival benefits[41,91,92]. It is undoubted that the multimodality current treatment plan is accompanied by the best outcomes of this otherwise lethal disease[40]. However, unfortunately, for the mutated *BRAF* gene wild type, there has not yet been effective treatment[4].

Since the recent innovation of targeted PD-1 and PD-L1 interaction by monoclonal antibodies atezolizumab, spartalizumab and pembrolizumab, the application of immunotherapy has been increasing[6,12,93]. It may be a promising therapeutic choice, especially in those with high PD-1 and PD-L1 expression without *BRAF* gene mutations[4,40,48,59,94]. Atezolizumab, a monoclonal antibody against PD-L1, gives encouraging results in combination with radiation therapy[31]. Spartalizumab and pembrolizumab are monoclonal antibodies against PD-1[4]. Spartalizumab has been used in a phase II clinical study in unresectable locally advanced or metastatic cases, showing a one-year survival of 40% and a median overall survival of 5.9 mo. Among the side effects, diarrhea, pruritus, fever, and fatigue have been reported[95]. Pembrolizumab has been used in likewise unresectable cases, showing a one-year survival of 38% and a median overall survival of 4.4 mo[96].

Various tumor experimental models of anaplastic thyroid carcinoma microenvironment in mice have been developed for scientific research and monoclonal antibody or other innovative drug production[30,97]. Novel promising therapies, including immunotherapy, multikinase inhibitors, aurora kinase inhibitors, gene therapy by oncolytic viruses, epigenetic modulators, and apoptosis-inducing agents, have been introduced[40,72,76,98,99].

Prognosis and survival

Early diagnosis and treatment yield the best outcome and prognosis[100-102]. A study from the United States including 719 patients found that racial, ethical and socioeconomic status seems to influence survival and prognosis. Nonwhite patients had a lower likelihood of receiving treatment and poorer survival; those living in high poverty had a worse prognosis[103]. A large cohort study from China including 735 patients with multidisciplinary management of anaplastic thyroid carcinoma found an overall survival of 10.7% at 2 years and 8.1% at 5 years. By stage, survival at 2 years was 36.5% (IVA), 15.6% (IVB), and 1.4% (IVC)[9]. A large single institution 20-year study from the United States including 479 patients with multimodality management of anaplastic thyroid carcinoma found a constantly increasing overall survival among three periods of treatment due to progression improvement by the addition of targeted therapy and immunotherapy. The overall survival for 2000-2013 was 35% at 1 year and 18% at 2 years; for 2014-2016, it was 47% at 1 year and 25% at 2 years; for 2017-2019, it was 59% at 1 year and 42% at 2 years[104]. A nationwide cohort study from the Netherlands including 812 patients with management of anaplastic thyroid carcinoma during the period 1989-2016 found a median overall survival of 2.2 mo, overall one-year survival of 12%, and one-year survival of 21.6% in those without distant metastases. Prognostic factors for better survival were age < 65 years, treatment based on more than two to three modalities, without distant metastases and bilateral lymph node involvement[5]. A recent large study including 5359 patients with anaplastic thyroid carcinoma found a total one-year survival of 23%[44]. A nationwide cohort study from Denmark including 320 patients with management of anaplastic thyroid carcinoma during the period 1980-2014 found a

Table 4 Predictive factors for favorable prognosis of anaplastic thyroid carcinoma

n	Factor
1	Female patients
2	Age ≤ 60 yr
3	Married patients
4	Asymptomatic patients
5	Tumor ≤ 5 cm in size
6	Single primary tumor
7	Without local tissue invasion
8	Without lymph node involvement (N0)
9	Without distant metastases (M0)
10	Kind of therapy
11	Multimodality treatment

1-year survival of 18% and a 5-year survival of 12%[2].

Another recent large study from China including 1080 patients with stage IVA: 6.3%, IVB: 21.9%, IVC: 71.8% anaplastic thyroid carcinoma management found disease specific survival at 1 mo of 83.1%, at 6 mo, 37.5%, and at 12 mo, 21%. The 1-year disease specific survival was 53.3% for stage IVA, 36.5% for IVB and 13.1% for IVC[35]. A recent study from a tertiary academic hospital in the United States including 45 patients found a median survival of 6.1 mo; smaller tumors and chemotherapy were related to better survival[105]. It was found by regression analysis that age, distant metastases and tumor size were independent factors of worse prognosis[106].

It was found by univariate analysis that distant metastases, lymph node involvement, tumor > 5 cm in size, and local infiltration were predictive factors for worse prognosis[107]. Multivariate analysis showed that the absence of both symptoms and distant metastases was related to longer survival. The asymptomatic patients were younger (≤ 60 years) and had smaller tumors (≤ 5 cm) than symptomatic patients with anaplastic thyroid carcinoma[108]. Another study found by multivariate analysis that age, sex, marital status, multiple primary tumors, distant metastases, and therapy type were independent prognostic factors for cancer-specific survival[109]. A recent large study from China including 1140 patients with anaplastic thyroid carcinoma management found an overall survival of 27.6% at 6 mo, 15.1% at 1 year, and 6.2% at 2 years. The age cutoff was 65 years as a significant predictive factor of improved survival[110]. The predictive factors for favorable prognosis are shown in Table 4.

It has been reported that age ≥ 65 years, palliative surgery and white cell count ≥ 10000/mm^3 are predictive factors for worse prognosis[67]. Despite proper management, recurrence with a high incidence may occur. An overall survival of 5-6 mo (specifically 9 mo for stage IVA, 4.8 mo for stage IVB and 3 mo for stage IVC) and a one-year survival of 20% have been reported[43]. Although, the overall prognosis of anaplastic thyroid carcinoma is very poor, in some cases is relatively good. There is evidence that patients with anaplastic carcinoma clearly transformed from papillary thyroid carcinoma, or those with mutated *BRAF* gene had a significantly better prognosis than other patients. Despite, the conflicting aspects for the above mentioned, it could be possibly explained by the higher expression of PD-L1 in papillary than in anaplastic carcinoma and response to immunotherapy[59] and anti-BRAF targeted therapy[24]. A long-term survival reaching above 5 years has been reported in isolated cases after surgical excision and adjuvant chemotherapy[18, 19].

CONCLUSION

Anaplastic thyroid carcinoma is a rare, rapidly growing and extremely aggressive neoplasm with a dismal prognosis. The correct early diagnosis and treatment are important perquisites for the management of an otherwise lethal condition. US and core needle biopsy are used to make the diagnosis. Preoperative imaging, histopathology and molecular testing establish an accurate natural status and determine the therapeutic strategy plan. Complete surgical resection with wide lymphadenectomy whenever possible is the main step followed by chemoradiation therapy, targeted therapy and immunotherapy. Palliation management may improve the quality of an otherwise unbearable life. Novel multimodal treatment that must be personalized offers the best chance to manage this incurable disease.

FOOTNOTES

Author contributions: Pavlidis ET, Galanis IN, and Pavlidis TE analyzed data, and reviewed; Pavlidis TE designed research, contributed new analytic tools; Pavlidis ET performed research and wrote the paper.

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MINIREVIEWS

Current perspectives on the management of lateral pelvic lymph nodes in rectal cancer

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Abstract

Significant controversies exist with regards to the optimal management of lateral pelvic lymph nodes metastases (mLLN) in patients with low rectal cancer. The differing views held by Japanese and Western clinicians on the management of mLLN have been well documented. However, the adequacy of pelvic lymph node dissection (PLND) or neoadjuvant chemoradiation (NACRT) alone in addition to total mesorectal excision (TME) have recently come into question, due to the relatively high incidence of lateral local recurrences following PLND and TME, or NACRT and TME alone. Recently, a more selective approach to PLND has been suggested, involving a combination of neoadjuvant therapy, followed by PLND only to patients in whom the oncological benefit is likely to outweigh the risk of potential adverse events. A number of studies have attempted to retrospectively identify certain nodal characteristics on preoperative imaging, such as nodal size, appearance, and size reduction following neoadjuvant therapy. However, no consensus has been reached regarding the optimal criteria for a selective approach to PLND, partly due to the heterogeneity and retrospective nature of most of these studies. This review aims to provide an overview of recent evidence with regards to the diagnostic challenges, considerations for, and outcomes of the current management strategies for mLLN in rectal cancer patients.

Key Words: Pelvic lymph node dissection; Lateral pelvic lymph nodes; Diagnostic criteria; Short axis diameter; Radiotherapy; Rectal cancer

Core Tip: The optimal management strategy for lateral pelvic lymph node metastases (mLLN) requires a multimodal approach, involving chemoradiation and pelvic lymph node dissection (PLND), in order to achieve adequate local control in patients with locally advanced low rectal cancer. This selective approach requires careful selection of patients who would benefit most from PLND, using pre-treatment nodal short axis measurements as a surrogate for mLLN risk.

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INTRODUCTION

Total mesorectal excision (TME) and the circumferential resection margin have been widely accepted as crucial elements in the surgical treatment of rectal cancer. However, the management of pelvic side wall disease remains controversial, and historically divergent between countries in the West and those in the far East. While the former predominantly recommend the use of radiotherapy (with or without chemotherapy), pelvic lymph node dissection (PLND) is preferred in the latter. This has been reflected in guidelines published by their respective societies[1-3].

Results from the Dutch TME trial[4] (10-year local recurrence (LR) rates of 5% in the irradiated group *vs* 11% in the non-irradiated group, $P < 0.0001$) and the Swedish Rectal Cancer Trial[5] (LR rate of 9% in the irradiated group *vs* 26% in the non-irradiated group, $P < 0.001$) supported the use of neoadjuvant radiotherapy. These rates were comparable to patients who underwent PLND in some Japanese studies. In contrast, early results of PLND in the West[6,7] were discouraging due to high perioperative morbidity and limited reported oncological benefit[8], resulting in its slow uptake.

In Japan, however, lower local failure rates (Dukes B cases 8.4% *vs* 26.1%, $P < 0.01$, Dukes C cases 24.5% *vs* 44.3%, $P < 0.01$) and improved 5-year survival (Dukes B cases 83.2% *vs* 63.7%, $P < 0.05$; Dukes C cases 52.5% *vs* 30.8%, $P < 0.05$) were reported when extended lymphadenectomy was performed[9]. In addition, PLND was only associated with a slight prolongation of operating time (additional 60 min), a modest increase in operative blood loss (additional 150 mL), and no increase in operative mortality[9].

This article aims to elucidate the factors contributing to the contrasting recommendations in the management of lateral pelvic lymph nodes (LLN), and to provide a more contemporary approach to this conundrum. Literature search was performed electronically using PubMed (MEDLINE) and the *Reference Citation Analysis* (https://www.referencecitation-analysis.com) was applied. The search terms were as follows: pelvic lymph node dissection or PLND, lateral lymph node metastasis, and rectal cancer in combination with Boolean operators AND and OR. All studies in English were extracted for review by the authors.

THE SIGNIFICANCE OF THE LATERAL PELVIC LYMPH NODES

The difference in lymphatic drainage of the lower rectum from the upper rectum has been well documented, with Gerota [10] describing how tumours in the mid and lower rectum appear to exhibit lateral lymphatic drainage into the iliac nodes in addition to upward drainage through mesorectal nodes[11,12].

The risk of developing lateral lymph node metastases (mLLN) in rectal cancer has been shown to vary with several factors. Distance from the anal verge has been reported to be inversely related to the risk of mLLN, with rates of up to 33.3% observed in tumours 3.9cm from the anal verge[13]. Locally advanced pT3 and pT4 tumours tend to also be associated with higher rates of mLLN[13]. In particular, it has been demonstrated that mLLN were mostly located in the group of nodes along the internal iliac artery (IIA), being the first draining basin from the lateral rectal ligaments[14-16].

Traditional TNM staging for rectal cancer classifies malignant deposits in the external iliac and obturator nodes as distant metastases[17]. On the other hand, the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma (3rd edition)[18], includes lymph nodes along the IIA, obturator, external iliac, common iliac (CIA), and median sacral arteries within its definition of regional lymph nodes, in the context of lower rectal cancers. This was based on survival data from the Japanese Nationwide Multi-Institutional Study on Lateral Pelvic Lymph Node Metastasis in Low Rectal Cancer[19]. Patients with metastasis to the above, so-called external lateral pelvic nodes, demonstrated more favourable overall survival and cancer-specific survival if they underwent PLND, than in patients with stage IV disease who underwent R0 resection (overall survival 29% *vs* 24%, $P = 0.0240$, cancer-specific survival 37% *vs* 27%, $P = 0.0117$). In addition, Ogura *et al*[20] determined that LLN enlargement did not appear to influence distant recurrence rate, suggesting that mLLN likely represent locoregional disease.

DIAGNOSTIC DILEMMAS – DIAGNOSTIC CRITERIA, MISDIAGNOSIS AND MISSED DIAGNOSES

However, epidemiological studies on mLLN suffer from the heterogenous methods used in evaluating nodal disease, with incidence rates being reported to range between 8.8% and 34%[13,21]. Studies that do not involve PLND would base their diagnosis on imaging, whereas analyses involving patients who had undergone PLND would report based on pathological confirmation. Most studies that evaluate recurrences in the pelvic side wall do so by means of imaging parameters.

The main challenge in preoperative radiological assessment of LLN lies in not missing occult metastases within the nodes (missed diagnoses), while minimising cases of misdiagnoses. Most imaging modalities have been evaluated for their diagnostic accuracy in detecting suspicious lateral pelvic nodes. Ultrasonography was suggested as a potential imaging modality for this purpose, but failed to adequately examine obturator nodes[22], and has largely been surpassed by other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Even then, the sensitivity of CT and MRI in detecting mLLN varies greatly between studies[23,24]. More recently, the accuracy of F-fluorodeoxyglucose positron-emission tomography (^{18}F-FDG PET) as a diagnostic adjunct in addition to CT or MRI has also been evaluated, although many guidelines do not include ^{18}F-FDG PET scanning as part of the initial staging for rectal cancer patients[2,25]. A study by Ishihara *et al*[26] evaluated the accuracy of ^{18}F-FDG PET scanning in identifying suspicious LLN post neoadjuvant chemotherapy, using a calculated maximum standard uptake value (SUV max) of 1.6, and reported an accuracy, sensitivity, and specificity of 85.7%, 76.5%, and 100% respectively. Metastatic LLN were found to have a significantly higher SUV max when compared to LLN without metastatic deposits (mean ± standard deviation 2.2 ± 1.3 *vs* 1.2 ± 0.3, $P < 0.01$). A similar study by Yukimoto *et al*[27] subsequently reported similar values (accuracy 92.3%, sensitivity 82.4%, specificity 93.4%) with a slightly lower SUVmax cutoff value of 1.5. These studies were mainly limited due to their small cohort size, and the utility of ^{18}F-FDG PET scanning in rectal cancer in most units has been mainly limited to the evaluation of equivocal findings on contrast-enhanced CT, or in patients with a strong contraindication to intravenous contrast[3]. As a result, the European Society for Medical Oncology and the American Society of Colon and Rectal Surgeons still recommend the use of pelvic MRI for locoregional staging[2,25].

Apart from the type of imaging modality, there also exists a lack of consensus in what imaging features constitute a suspicious LLN, or mLLN. Table 1 summarises the various criteria used. Most studies retrospectively identify short (SAD), or long axis diameter (LAD) measurements and nodal features that correlate with pathological nodal metastases and/or oncological outcome. The multi-national Society of Abdominal Radiology – Rectal & Anal Cancer Disease-Focused Panel recently published a consensus statement[28] to promote consistent terminology and reporting standards amongst abdominal radiologists. The consensus statement recommended internal iliac and obturator nodes with SAD > 7 mm be reported as suspicious[28]. The MERCURY[29] study reviewed the preoperative MRI images of patients with biopsy-proven rectal adenocarcinoma within 15cm from the anal verge who underwent TME without PLND. The nodes were considered suspicious based on the presence of mixed signal intensity and/or an irregular nodal capsule border.

Further contributing to the heterogeneity is the inconsistent use of pre- or post-neoadjuvant imaging, or a combination of both sets of imaging (reflecting the response to neoadjuvant treatment). Akiyoshi *et al*[30] showed that the incidence of occult mLLN was as high as 20% even in patients with a post-neoadjuvant nodal size of 5 mm or less, supporting the recommendation of basing further treatment selection on pre-neoadjuvant imaging.

With regards to post-neoadjuvant nodal size, Cribb *et al*[31] found that a SAD of 5 mm on post-treatment MRI was associated with a worse 3-year local recurrence-free survival [hazard ratio (HR) 8.35, $P = 0.001$]. Malakorn *et al*[32] concluded that a post-neoadjuvant nodal size of 5 mm was 100% sensitive for identifying patients with mLLN and as such recommend using a post-neoadjuvant LLN size cutoff of 5 mm for PLND. The high reported sensitivity of a post-treatment nodal SAD of 5 mm is promising and has been recommended as suitable criteria for PLND[32,33]. In addition, the Lateral Node Study Consortium demonstrated that PLND can be safely omitted in patients with LLN measuring 4mm or less on restaging MRI due to the negligible risk of lateral local recurrence at 3 years in this subgroup of patients[14].

Akiyoshi *et al*[30] analysed patients with cT3/4 rectal cancers who underwent either bilateral (15.6%) or unilateral (84.4%) PLND, based on a nodal LAD cutoff of 7 mm on pre-neoadjuvant CT or MRI. Pathological mLLN were found in 40.3% of patients, and persistent LLN on restaging was associated with a higher rate of metastatic deposits when compared with LLN that responded to neoadjuvant chemoradiotherapy (CRT) (75% *vs* 20%, $P < 0.0001$)[30].

In publications reporting pathological results, incidence rates can also be confounded by potential missed diagnoses. The identification of micrometastatic disease or isolated tumour cells may sometimes pose a diagnostic challenge. Miyake *et al*[34] compared the sensitivity of one-step nucleic acid amplification assay results to conventional histological diagnosis, and identified a number of additional histologically-negative nodes with metastatic disease. Limitations in commonly utilised histological processing methods may have resulted in a small proportion of missed diagnoses of mLLN, with failure to pathologically upstage such patients resulting in adverse prognostic implications.

THE ADEQUACY OF PLND OR/AND CHEMORADIATION

While the efficacy of neoadjuvant CRT in reducing LR rates have been well documented[4,5], lateral pelvic recurrences have nonetheless been reported in cases where PLND was omitted after CRT[35]. Kim *et al*[36] reported a 64.6% lateral local recurrence (LLR) rate, out of a 7.2% LR rate following pre or post-operative chemoradiotherapy, after a median follow-up period of 65 mo. Kusters *et al*[37] similarly reported a 64.3% LLR rate and 18.7% LR rate. Both studies concluded that LLN measuring 10 mm were associated with an increased risk of recurrence and poorer overall survival, and that CRT alone in these patients did not confer adequate local control.

Table 1 Summary of diagnostic criteria for suspicious lateral pelvic lymph nodes

Study	Imaging modality	Nodal size	Nodal features
Schaap *et al*[53], 2021	MRI	Pre-treatment: SAD 7 mm	-
Amano *et al*[23], 2020	MRI; CT; PET-CT	(MRI or CT) SAD > 6 mm; (PET/CT) increased FDG uptake	-
Kim *et al*[54], 2020	MRI	Pre-treatment: SAD 7 mm; Post-treatment: SAD 4 mm	-
Lee *et al*[55], 2019	CT or MRI	Pre-treatment: SAD 8 mm	-
Sapci *et al*[56], 2019	MRI	Size > 5 mm	And either heterogeneity or border irregularity
Schaap *et al*[57], 2018	MRI	SAD 10 mm	-
Kim *et al*[58], 2018	MRI	Pre-treatment: SAD 5 mm	Signal intensity homo/heterogenous; Margins irregular or well defined; DWI signal intensity high or low; Size reduction rate
Akiyoshi *et al*[30], 2015	MRI	Pre-treatment: SAD 8 mm	-
Kobayashi *et al*[59], 2015	CT	LAD > 9 mm; SAD > 6 mm	-
Ogawa *et al*[60], 2015	MRI	SAD 10 mm or 5 mm (institution-dependent)	Enlarged LPLN on palpation; Enlarged perirectal node or LPLN 5 mm
Ogawa *et al*[61], 2014	MRI	LAD 5 mm; LAD < 5 mm	-
Shihab *et al*[29], 2011	MRI	No size criteria	Mixed signal intensity or irregular nodal capsule border
Matsuoka *et al*[62], 2007	MRI	LAD 10 mm; SAD 5 mm	Ovoid shape; heterogeneity

CT: Computed tomography; MRI: Magnetic resonance imaging; LAD: Long axis diameter; SAD: Short axis diameter; LPLN: Lateral pelvic lymph node.

On the other hand, the Japanese JCOG0212[38-40] randomised controlled trial illustrated the impact of bilateral prophylactic PLND alone, without the use of CRT, even though adjuvant chemotherapy was prescribed to pathological stage III patients. Only patients without clinically suspicious LLN nodes (SAD 10 mm on CT/MRI) were enrolled. The study reported that the addition of PLND resulted in a statistically significant reduction in LR rates (7.4% *vs* 12.6%, P = 0.024), and a higher local recurrence-free survival of 85.3%, compared to 80.3% with TME alone. The authors therefore concluded that the trial failed to demonstrate the noninferiority of TME alone, even though the significant reduction in LR may have resulted from the SAD cutoff of 10mm being insufficiently sensitive in predicting for mLLN. Nonetheless, the 7% incidence of occult mLLN in this trial suggests that a significant proportion of patients were subjected to the morbidity of PLND without deriving any oncological benefit.

Other studies evaluated the impact of combining the two treatment modalities. Kim *et al*[35] retrospectively analysed 366 patients with cT3/4 tumours within 8 cm from the anal verge who received CRT prior to TME without PLND. They reported a LR rate of 7.9% after a median follow-up duration of 40.1 mo, with 82.7% of these being LLR. Conversely, the addition of PLND to TME significantly reduced LR rates despite prior CRT (CRT+TME 19.5% *vs* CRT+TME+PLND 5.7%, P = 0.042)[20].

A three-armed multinational study by Kusters *et al*[41] compared patients with rectal cancer from the Netherlands and Japan who underwent either: (1) TME alone; (2) TME with (neo)adjuvant radiation; or (3) TME with PLND. Similar overall LR rates were reported between groups (2) and (3) (RT+TME 5.8% *vs* 6.9% PLND+TME, HR 1.0 (0.6-1.8). Only group (1) had a higher 5-year LR rate of 12.1%.

Recently, a multicentre retrospective study by Ogura *et al*[14] found that nodes along the internal iliac artery were less responsive to chemoradiation, and concluded that IIA nodes measuring 7 mm or more on pre-treatment MRI were predictors of lateral local recurrence. The study reported 5-year LLR rates of 52.3% following neoadjuvant chemoradiotherapy and TME surgery but without PLND[14]. When PLND was performed, the 5-year LLR risk was significantly reduced to 8.7% (P = 0.007)[14].

SELECTIVE PLND POST NEOADJUVANT RADIOTHERAPY

The optimal management of mLLN appears to therefore be shifting towards a selective multimodal approach, with selective PLND post neoadjuvant therapy appearing to offer higher rates of local control in several studies. Numerous variables have been proposed as potential indications for PLND due to their reported sensitivities in identifying occult mLLN, and their prognostic implications. In addition to the aforementioned studies, Akiyoshi *et al*[42] reviewed patients with stage II-III low rectal cancer who underwent preoperative CRT prior to surgery. PLND was performed in patients with suspicious LLN on pre-neoadjuvant CT or MRI, using SAD criteria of ≥ 7 mm[42]. Patients with clinically enlarged LLN underwent PLND irrespective of findings on post-treatment restaging[42]. The study observed that no LLR occurred in patients who underwent PLND, while 3.4% of patients who only underwent TME post chemoradiation developed LLR [42]. A similar study by Ishihara *et al*[43] reported similar findings. PLND was again performed based on the presence of suspicious pre-neoadjuvant nodes, irrespective of their response to neoadjuvant treatment[43]. The study reported LLR rates of 0% and 0.9% in patients who underwent TME with PLND and TME only respectively[43], suggesting that the selective addition of PLND is key in achieving local control in the lateral pelvis. Therefore, suspicious internal iliac or obturator nodes with pre-treatment SAD of ≥ 7 mm, or the presence of nodes displaying heterogeneity and/or irregular borders, should form indications for PLND.

TECHNICAL CHALLENGES OF PLND

In the treatment of rectal cancer, PLND typically involves removal of nodes in the internal iliac and obturator compartments[44]. The JCOG0212 trial concluded that the addition of PLND was associated with a significantly longer operative time (median 360 min *vs* 254 min, $P < 0.0001$) when compared to TME alone, and was associated with more intraoperative blood loss (576 mL *vs* 337 mL, $P < 0.0001$)[45]. No statistically significant differences were reported with regards to the incidence of anastomotic leakage ($P = 0.46$), urinary retention ($P = 0.18$), wound infection ($P = 0.81$), pelvic abscess ($P = 0.29$), or bowel obstruction ($P = 1.00$)[45]. A meta-analysis of extended lymphadenectomy *vs* conventional surgery for rectal cancer found similar results, with no significant differences in perioperative mortality ($P = 0.63$) or morbidity ($P = 0.13$)[46].

In a bid to promote the safe implementation of PLND, Ngu *et al*[47] conceptualised the use of origami to convert the pelvic side wall from a 2-dimensional region into a 3-dimensional compartment made up of two triangular pyramids. The authors sought to simplify PLND into a procedure involving three planes, three boundaries, and three steps. The three planes consisted of: (1) The ureterohypogastric nerve fascia (UHNF); (2) the vesicohypogastric fascia; and (3) the external iliac muscular plane. Following medialisation of the UHNF, the proximal boundary is marked by two key landmarks: superficially where the ureter crosses the CIA and, at a deeper plane, the bifurcation of the common iliac vein, where the obturator nerve enters the pelvic sidewall compartment. The distal boundary is delineated superficially by the vas deferens or round ligament, and, at a deeper level, the obturator foramen. The third (deep) boundary is marked by the terminal branches of the internal iliac vessels. The three steps of PLND involve: (1) The separation of these three planes, (2) followed by the delineation of the three boundaries, and (3) finally the dissection of the internal iliac vessels, with en bloc removal of the lympho-fatty tissue.

Tang *et al*[48] compared the short-term outcomes of laparoscopic PLND against open PLND, and concluded that laparoscopic PLND was associated with a shorter operative time (255 min *vs* 300 min, $P = 0.001$), less intraoperative blood loss (50 mL *vs* 300 mL, $P < 0.001$), lower incidence of postoperative complications (32% *vs* 15%, $P = 0.005$), shorter postoperative hospital stay (8 *vs* 14 d, $P < 0.001$), and excision of more lateral pelvic nodes (9 *vs* 7 nodes, $P = 0.025$) when compared to open PLND. Oncological outcomes were similar, with no differences reported in 3-year overall survival ($P = 0.581$) and disease-free survival ($P = 0.745$) rates[48]. Aside from the aforementioned postoperative complications, this study also reported other surgical complications such as chylous ascites and lower limb neuropathy, as well as systemic complications such as renal failure, pneumonia, and arrhythmias[48].

Utilization of the robotic platform in PLND has recently been shown to result in lower blood loss (25 mL *vs* 637 mL, $P < 0.0001$) and less postoperative complications including wound infection, anastomotic leakage, urinary retention, and small bowel obstruction when compared to open PLND, but operative times were longer (455 min *vs* 410 min, $P < 0.007$) [49]. Robotic PLND was also associated with superior 5-year local relapse-free survival rates compared to open PLND (98.6% *vs* 90.9%, $P = 0.029$), with similar overall survival (robotic 95.4% *vs* open 87.8%, $P = 0.106$) and relapse-free survival rates (robotic 79.1% *vs* open 69.9%, $P = 0.157$)[50]. Although PLND is a technically demanding procedure with significant risk of associated morbidity, robotic or laparoscopic assistance may be useful adjuncts, associated with lower postoperative morbidity rates when performed by experienced surgeons.

Although not traditionally a recordable perioperative morbidity, the potential of missed nodes during PLND may result in poorer oncological outcomes. A novel strategy to potentially mitigate the risk of intraoperatively missed nodes during PLND is the utilisation of indocyanine green (ICG) during laparoscopic PLND[51,52]. Ohya *et al*[52] conducted a retrospective study of patients who underwent PLND for tumours cT3 and above with clinically suspicious lateral pelvic nodes on pre-op imaging. The study demonstrated an increased lymph node yield (ICG 14 *vs* no ICG 9, $P < 0.001$), without a substantial difference in post-operative complications ($P = 0.57$), aside from a longer operative time (ICG 426 min *vs* no-ICG 369 min, $P < 0.001$). ICG use was also associated with a significant reduction in intraoperative blood loss (13 mL *vs* 100 mL, $P = 0.001$). The authors recently published their long-term follow-up data, and the higher lymph node yield with ICG translated into a reduction in 3-year cumulative LR rates (ICG 0% *vs* no-ICG 9.3%, $P = 0.048$), although no statistically significant difference was reported in relapse-free survival and overall survival rates[51].

CONCLUSION

The difficulty in reaching a global consensus with regards to the optimal management of LLN in rectal cancer stems from the heterogeneity of available data, mainly consisting of retrospective cohort studies using various parameters to define what constitutes a clinically suspicious LLN, or mLLN. Contemporary data appears to suggest that the optimal strategy may lie somewhere between the traditional views held by Western countries and the far East. Several conclusions can be drawn from the existing data: Firstly, pelvic lymph node dissection in rectal cancer has to offered selectively. The JCOG0212[38-40] study demonstrated that in the absence of radiologically suspicious nodes, the majority of patients would not benefit from PLND, hence justifying a more selective, non-prophylactic approach to PLND. Secondly, the optimal management strategy for mLLN in patients with rectal cancer requires a multimodal approach, involving a combination of neadjuvant chemoradiation and selective PLND. Thirdly, until more robust data is made available, a prudent choice would be to use a SAD of 7 mm, or the presence of suspicious features, as criteria for selective PLND. This assessment should be made based on pre-neoadjuvant MRI.

FOOTNOTES

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MINIREVIEWS

Anti-tumor effect of coix seed based on the theory of medicinal and food homology

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Abstract

Coix seed is a dry and mature seed of *Coix lacryma-jobi L.var.ma-yuen (Roman.) Stapf* in the Gramineae family. Coix seed has a sweet, light taste, and a cool nature. Coix seed enters the spleen, stomach, and lung meridians. It has the effects of promoting diuresis and dampness, strengthening the spleen to prevent diarrhea, removing arthralgia, expelling pus, and detoxifying and dispersing nodules. It is used for the treatment of edema, athlete's foot, poor urination, spleen deficiency and diarrhea, dampness and obstruction, lung carbuncle, intestinal carbuncle, verruca, and cancer. The medicinal and health value is high, and it has been included in the list of medicinal and food sources in China, which has a large development and application space. This article reviews the current research achievements in the processing methods and anti-tumor activities of Coix seed and provides examples of its clinical application in ancient and modern times, aiming to provide reference for further research on Coix seed and contribute to its clinical application and development. Through the analysis of the traditional Chinese patent medicines, and simple preparations and related health food of Coix seed queried by Yaozhi.com, the source, function, and dosage form of Coix seed were comprehensively analyzed, with a view of providing a reference for the development of Coix seed medicine and food.

Key Words: Coix seed; Cancer; Tumor; *Coix lacryma-jobi L.var.ma-yuen (Roman.) Stapf*; Medicinal herbs

Core Tip: Cancer is a serious disease that causes a huge economic and social burden worldwide. In addition, cancer has become one of the biggest health threats globally. Numerous studies have confirmed that Coix seed has anti-tumor effects. This article will review its preparation, anti-tumor effects, and edible value.

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INTRODUCTION

Cancer is a serious disease that causes a huge economic and social burden worldwide. An estimated 19.3 million new cancer cases and nearly 10 million cancer deaths were reported in 2020. It is expected that the global cancer burden will reach 28.4 million cases by 2040, an increase of 47% compared to 2020[1]. In addition, cancer has become one of the biggest health threats globally. Therefore, how to effectively prevent and treat cancer has become a global focus of attention[1]. So, exploring effective cancer treatment measures is crucial.

Medicinal and food-dual-use foods can be consumed as both delicious foods and medicinal herbs for treating diseases. They belong to traditional Chinese medicine and have good therapeutic effects. They are also nutritious and delicious foods that people often eat. Coix seed, which can be used as both food[2]and medicine[3], is an important raw material for the development of food or health food. Coix seed is a good medicine and food for dispelling dampness and strengthening the spleen.

At present, Chinese herbal medicine[4] has significant effects in inhibiting cancer proliferation, metastasis, inducing cell apoptosis[5], blocking the cell cycle, alleviating pain[6], improving quality of life[7], and has received widespread attention from researchers[8,9]. Numerous studies have confirmed that Coix seed has anti-tumor effects. This article will review its preparation, anti-tumor effects, and edible value (Figure 1).

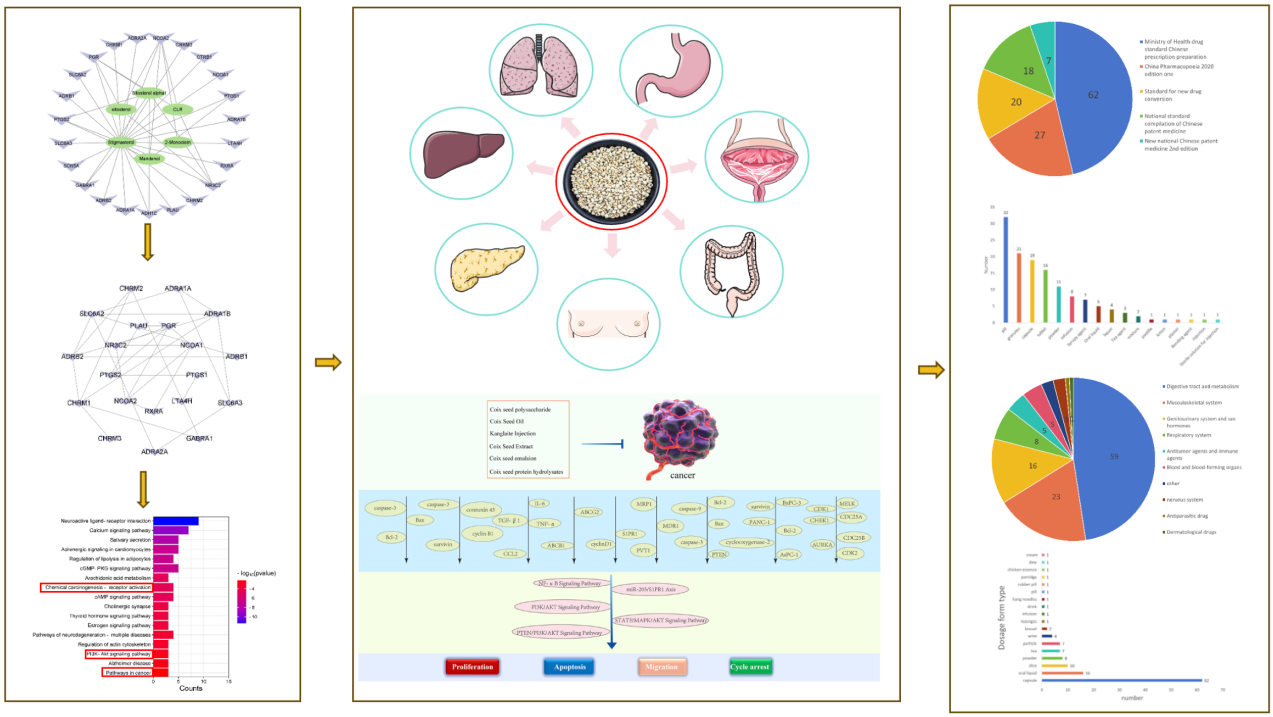

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Figure 1 Flow chart.

BRIEF INTRODUCTION

Coix seed, also known as Xie Li, Qishi, Ganmi, *etc*, is a dry and mature seed of *Coix lacryma-jobi L. var.ma-yuen (Roman.) Stapf* in the gramineae family[10]. Most regions in China produce it, mainly in Fujian, Hebei, and Liaoning. It is commonly found near houses, in the wilderness, by rivers, in streams, or in damp valleys. Coix seed has a sweet and light taste and a cool nature. It enters the spleen, stomach, and lung meridians. As a drug, it has the effects of promoting diuresis and dampness, strengthening the spleen[11] to stop diarrhea, removing arthralgia, expelling pus, and detoxifying and dispersing nodules. It can treat edema, athlete's foot, poor urination, spleen deficiency and diarrhea, dampness and obstruction, lung carbuncle, intestinal carbuncle, verruca, cancer[12,13], *etc*. As a food, its developed products have functions[14,15] such as increasing bone density, improving sleep, immune regulation[16,17], weight loss [18], regulating blood lipids and blood sugar, improving gastrointestinal function, anti-fatigue, promoting growth and development, improving memory, antioxidant[19], delaying aging, and protecting liver damage[20].

PROCESSING

Coix seed has a long history of and has various methods of processing[21]. Since the Northern and Southern Dynasties, there have been records of two processing methods: Glutinous rice stir frying and salt soup boiling. Subsequently, the Song Dynasty first proposed the stir frying method. Salt frying was added in the Ming Dynasty. During the Qing Dynasty, local stir frying was added. So far, commonly used processing methods such as stir frying, earth frying, bran frying, and sand frying have been recorded in the modern Chinese Pharmacopoeia and national and provincial processing standards (Table 1).

THE ANTI-TUMOR EFFECT OF COIX SEED

Screening of active ingredients and targets in Coix seed

We used Coix seed as a keyword to search on the TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, https://old.tcmsp-e.com/index.php)[22]. The active ingredients and their related action targets were picked according to the criteria of oral bioavailability[23] ≥ 30% and drug-likeness ≥ 0.18. Then, we translated the name into Gene Symbol format to obtain target genes for the main active ingredients of Coix seed *via* Uniprot database (https://www.uniprot.org/). We imported the active ingredients and their targets of Coix seed into Cytoscape 3.9.1 software to draw an "active ingredient-target" network. Next, we imported drug targets into the STRING database (http://string-db.org), species limited to "*Homo sapiens*", to retrieve protein-protein interaction relationships, and imported them into Cytoscape 3.9.1 software to create a network diagram. Through the Metascape database (https://metascape.org/), we conducted the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis on the target. The results of KEGG signal pathways are introduced into the Bioinformatics database (http://www.bioinformatics.com.cn/) and presented in the form of a bar chart and selected pathways related to cancer (Figure 2). The KEGG results indicate that the Coix seed target is associated with multiple cancer pathways and can effectively combat cancer. So, the next main analysis is the anti-tumor effect of Coix seed.

Anti-cancer effect of Coix seed and its components

Coix seed is a commonly used clinical drug with activities such as anti-tumor (Figure 3), immune regulation[24,25], hypoglycemic[26,27], anti-inflammatory[28,29], improving intestinal microbiota[17,30], lowering blood lipids[31,32], and promoting angiogenesis[33]. After KEGG enrichment analysis, we mainly discuss the pharmacological effects of Coix seed on anti-tumor effects (Table 2). Studies have confirmed that Coix seed and its extract can reduce the proliferation, invasion and migration of lung cancer[34], colon cancer, liver cancer, breast cancer, cervical cancer, gastric cancer, pancreatic cancer and other cancers, and can promote their apoptosis (Figure 4).

Lung cancer: Coix seed has a prominent inhibitory healing effect on lung cancer metastasis, and can inhibit proliferation and promote apoptosis. Research has shown that Paclitaxel combined with Kanglaite (KLT) can significantly improve patients' physical fitness, reduce bone metastasis area and tumor weight, and have significant effects in clinical treatment [35]. MiRNA-21 is a therapeutic effect indicator for lung cancer. By comparing the changes in indicators before and after treatment with KLT, the expression of miRNA-21 is reduced, indicating that KLT has a significant therapeutic effect on advanced lung cancer[36]. After cell experiments, Coix Polysaccharides can significantly inhibit the proliferation of lung cancer cells, and may induce apoptosis of lung cancer cells by increasing the expression of caspase-3 and caspase-9 genes [37]. KLT has significant anti-tumor activity in Lewis lung cancer mice, and when combined with cisplatin, it can improve chemotherapy efficacy and immune function by reducing TAM levels and improving hypoxia status[38]. Other studies have confirmed that Coix polysaccharides can demonstrably inhibit the migration and invasion of A549 cells *in vitro* cell experiments, and its molecular mechanism may be the down-regulation of S100A4 gene and protein expression levels[39].

Colon cancer: Research has shown that Coix seed performs well in combating colon cancer, blocking cell cycle, promoting apoptosis, and synergistic effects to achieve the effect of inhibiting colon cancer. On the HT-29 colon cancer cell model, the anticancer effect of Coix seed oil is dose-dependent and time-dependent. With the increase of drug concentration and the passage of time, the survival rate of tumor cells will also decrease[40]. The synergistic effect of paclitaxel treatment

Table 1 Processing method of Coix seed

Coix seed	Processing method	Source
Coix seed	Remove imports	Chinese Pharmacopoeia (2020)
Fried coix seeds	Clean the mix seeds and fry them until they are slightly yellow	Processing Standards of TCM Decoction Pieces in Hubei Province (2018)
Fried mix seed with bran	Clean the mix seeds and fry them with bran until they are slightly yellow	Chinese Pharmacopoeia (2020)
Fried coix seed in clay	Take the pure Coix seeds and fry them according to the method of soil frying until the surface benefits burn yellow and bulks up to the degree	Processing standard of TCM detection pieces in Henan Province (2005)
Coix seed powder	Take coix seeds, remove impurities and crush them into fine powder	Processing Standards of TCM Decoction Pieces in Sichuan Province (2015)
Jiao coix seed	Fry until browned	Processing Standards of TCM Decoction Pieces in Tianjin (2018)
Scald coix seed	Take the coix seed, wash it, moisten it thoroughly, steam it, dry it, and press it with the oil and method until it looks like a bubble	Fujian Province Traditional Chinese Medicine Processing Standards (1988)

TCM: Traditional Chinese medicine.

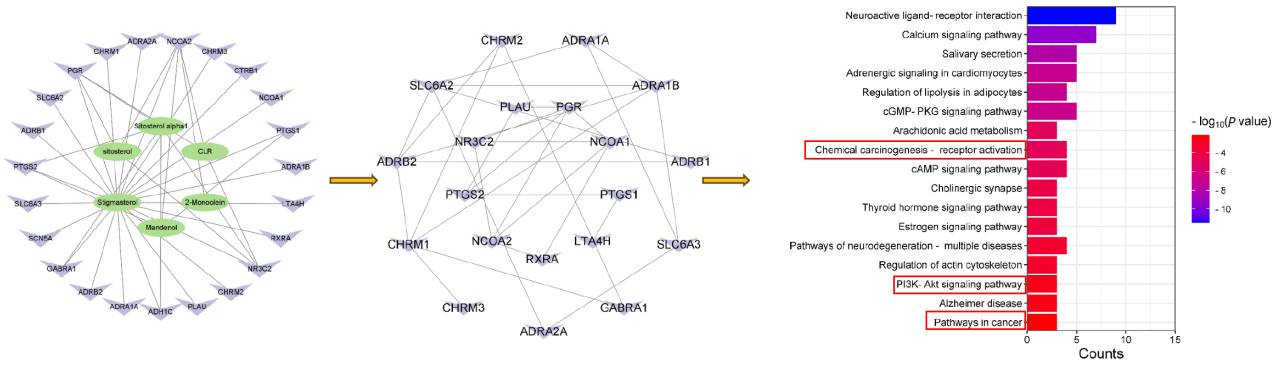

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Figure 2 Relationship between active components of Coix seed and cancer.

after pretreatment with KLT is the best, and KLT inhibits nuclear factor NF-κB and upregulates the expression of connexin 43, making cancer cells sensitive to paclitaxel[41], thereby exerting an inhibitory effect on colon cancer cells.

Liver cancer: The components of Coix seed have good therapeutic effects on liver cancer, and an efficient and safe anticancer drug delivery system has been developed. There have been studies on injecting KLT into transplanted liver tumors in rats and evaluating its impact, pros and cons. Research has shown that injecting KLT into implanted hepatocellular carcinoma is more effective than ethanol, and KLT has fewer side effects on liver function than ethanol[42]. In the study, Wang *et al*[43] discovered that the combination of Norcantharidin and Coix seed oil can exert anti-tumor efficacy by regulating the immune system. Coix seed components have an inhibitory effectiveness on the progression of liver tumors in nude mice and have minimal toxicity to the liver and kidneys[44]. Bitargeted microenvironments based on Coix seed receptors can effectively target tumors, enhance their inhibitory effect on tumor proliferation, and induce cancer cell apoptosis, thereby prolonging patient survival time[45].

Breast cancer: Coix seed oil has a large scale anti-cancer effect. Ting F found that Coix seed oil has a great inhibitory effect on triple negative breast cancer, which inhibited the proliferation and growth of triple negative breast cancer[46]. The results of network pharmacology and *in vitro* experiments show that KLT has an inhibitory effect on triple negative breast cancer, which can inhibit cell proliferation and invasion, block cell cycle and induce cell apoptosis. Its mechanism of action may be to block G2/M phase cells and downregulate G2/M phase related genes[47].

Cervical cancer: Microemulsions containing Coix seed components exhibit good anti cervical cancer effects, leading to cell cycle arrest and apoptosis, and to cancer cell death. Dissolving paclitaxel in Coix seed oil, the two synergistically fight cancer, exert stronger *in vitro* cytotoxicity, and induce cell apoptosis, which has a stronger therapeutic effect on cervical cancer[48]. Joint application of Coix Seed Oil and Tripterine can work synergistically on the proliferation of cervical cancer, as well as anti-angiogenesis and induction of cell apoptosis. In mouse models, minimal toxicity to important

Table 2 Anti-cancer effect of Coix seed and its components

Pharmacological effect	Ingredient	Conclusion
Lung cancer	Kanglaite	Paclitaxel combined with kanglaite is effective in improving bone metastasis of lung cancer
	Kanglaite injection	Kanglaite injection can significantly reduce the expression of miRNA-21 in patients with advanced lung cancer, and has a good thermal effect
	Kanglaite	Kanglaite can achieve benefits by reducing TAM levels and improving hypoxia in mice with Lewis lung cancer
Colon cancer	Coix seed oil	Coix seed oil plays an anti-colon cancer role by inducing G2 rest and topology of HT-29 cells by regulating PI3K/AKT signaling pathway
Colorectal cancer	Kanglaite injection	Kanglaite pretreatment may increase the effect of Taxol on colored cancer
Hepatoma	Coix seed components	Octanoyl galactose ester modified microemulsion system self-assembled by coil seed components to enhance tumor targeting and hepatoma therapy
	Coix seed ingredients	Bitargeted microemissions based on Coix seed ingredients have the effect of enhancing life tube transmission and synergistic therapy
Triple negative breast cancer	Kanglaite injection	Kanglaite injection was confirmed to have anti TNBC effects by arresting cell cycle and inhibiting CDK1 precipitation
	Coix seed oil	Coix seed oil exerts an anti-triple negative breast cancer effect by interrupting miR-205/S1PR1 axis
Clinical cancer	Coix seed oil	Self-enhancing system colored with paclitaxel and Coix seed oil deeply penetrated can enhance efficiency of clinical cancer
	Coix seed oil	Transferrin modified microemulsion carrying Coix seed oil and tripterine (Tf CT MEs) can be used to improve tube specific accumulation and connection to enhance clinical cancer treatment
	Coix seed oil	Coix seed oil and tripterine coated microemissions with a transfer modification (Tf CT MES) could improve the treatment of cervical cancer
Gastric cancer	Kanglaite injection	Kanglaite inhibits the expression of drug resistance genes through suppressing PVT1 in cisplatin-resistant gas cancer cells
Pancreatic cancer	Coix seed oil	Coix seed oil regulations mitochondrial functional image to induce apoptosis of human pancreatic cancer cells *via* the PTEN/PI3K/AKT signaling pathway
	Coix seed extract	Coix seed extract could augment the efficiency of gemcitabine therapy in pancreatic cancer cells
	Coix seed emission	Coix seed emission synergistically enhances the antagonist activity of gemcitabine in pancreatic cancer through inhibition of NF- κ B signaling
Ameliorates cancer cachexia	Coix seed oil	Coix seed oil ameliorates cancer cachexia by counteracting muscle loss and fat lipolysis

TNBC: Triple negative breast cancer.

organs was detected[49,50].

Gastric cancer: Coix seed can reduce the vitality of gastric cancer cells, promote cell apoptosis, and upgrade the quality of life. The reason of KLT regulating chemotherapy resistance in gastric cancer cells may be through regulating expression of MDR1 and MRP1 to inhibit cell viability and promote cell apoptosis. KLT can alleviate the development of multiple drug resistance (MDR) and participate in the potential mechanism of MDR in gastric cancer[51]. Comparing the indicators before and after treatment, the study found that patients with advanced gastric cancer treated with KLT combined with chemotherapy had reduced cancer, reduced chemotherapy side effects, and a further improved quality of life[52].

Pancreatic cancer: Coix seed can promote apoptosis of pancreatic cancer cells, make it sensitive to treatment, and enhance the therapeutic effect. Coix seed oil may adjust mitochondrial dysfunction and induces apoptosis in PANC-1 PC cells through PTEN, which may be related to the down-regulation of p-AKT and p-PI3K protein expression by Coix seed oil [53]. Coix seed extract can synergistically reinforce the anti-pancreatic cancer effect of Gemcitabine, significantly alleviate the up regulation of ABCB1 and ABCG2 proteins caused by the use of Gemcitabine, and detect strong correlation between Bioluminescence pharmacokinetic parameters and pharmacodynamic indicators and anti-tumor efficacy[54]. The anti-tumor effect of Coix seed emission combined with Gemcitabine is superior to that of any drug alone, and its mechanism is that Coix seed emission can eliminate the activation of NF-κB, making pancreatic cancer cells sensitive to gemcitabine therapy[55].

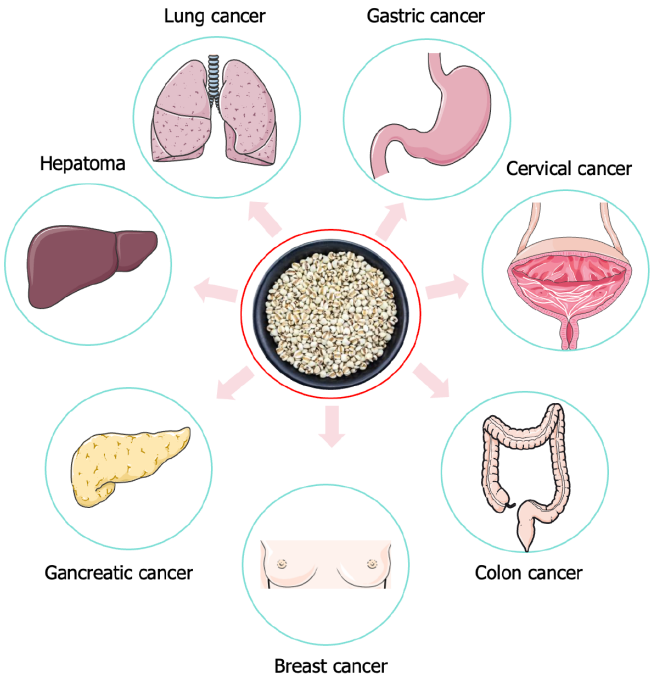

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Figure 3 Relationship between Coix seed and cancer.

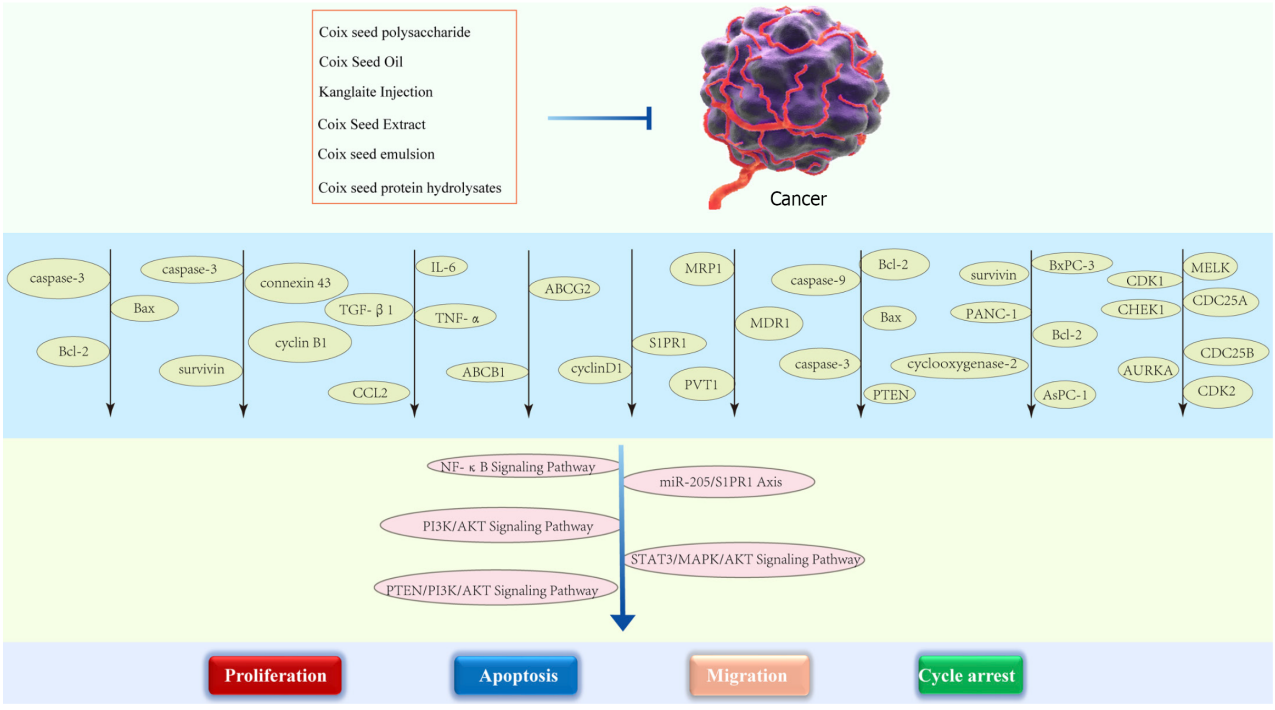

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Figure 4 Mechanism of anti-tumor action of Coix seed and its components.

Improving cancer cachexia: Researchers have found that administering Coix seed oil can significantly prevent weight loss and improve systemic inflammation in mice, without affecting food intake and tumor size. The results indicate that Coix seed oil can cause muscle and adipose tissue loss caused by cancer cachexia[56]. The results of clinical research on the injection of Coix seed oil into patients showed that Coix seed oil can effectively control the degree of pain, alleviate adverse reactions such as constipation and nausea, and raise the quality of life[57].

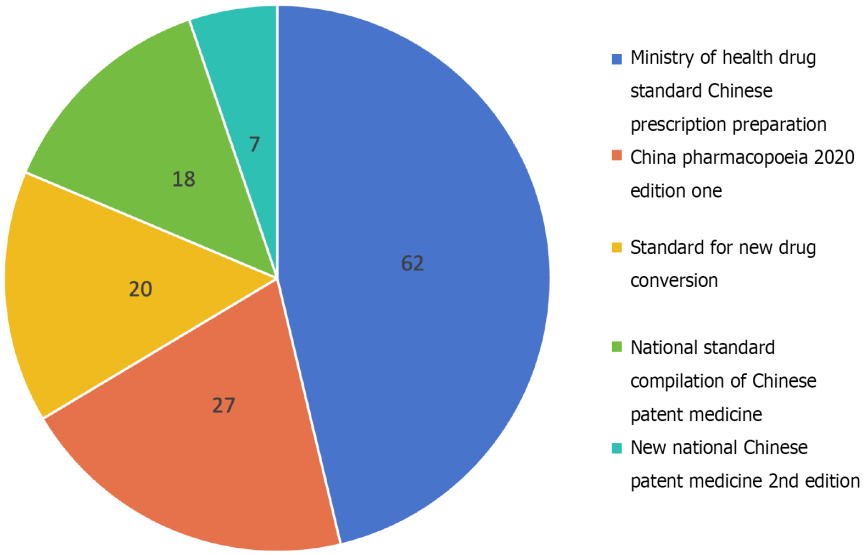

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Figure 5 Source and quantity of Chinese patient medicine containing Coix seed.

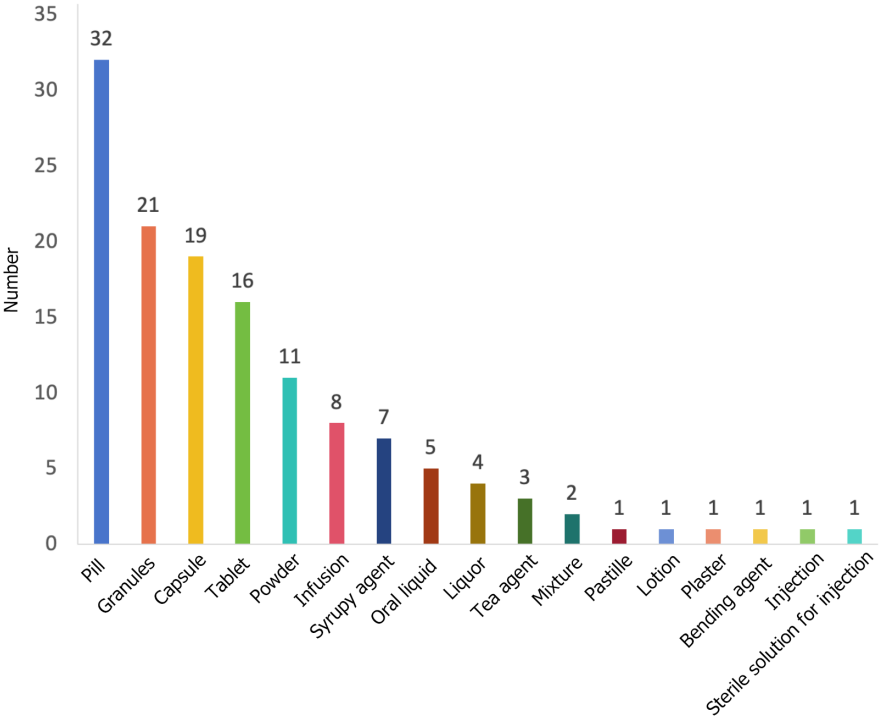

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Figure 6 Chinese medicine dosage form containing Coix seed.

APPLICATION OF COIX SEED

The medicinal value of coix seed

Coix seed has been widely applied since ancient times, and formulas containing Coix seed have also been widely used. Yiyi Fuzi Baijiang Powder can slow down the progression of colorectal cancer by simultaneously regulating target genes and related signaling pathways of multiple active ingredients, possibly by regulating cell apoptosis, cell proliferation, and protein and enzyme binding[58], and this has been experimentally validated[59]. Yiyi Fuzi Baijiang Powder has a good effect in treating ulcerative colitis, can inhibit intestinal symptoms in mice, and improve intestinal pathology[60]. According to reports, Qingyi huaji decoction can be applied as a valid method to treat pancreatic cancer, and research has confirmed that it can inhibit the growth and progression of tumor through various mechanisms such as anti-inflammatory and induction of cell apoptosis[61]. Shenling Baizhu Powder inhibits colitis related colorectal cancer by inhibiting epithelial mesenchymal transformation and myelogenous inhibitor infiltration, and reduces mortality by reducing the

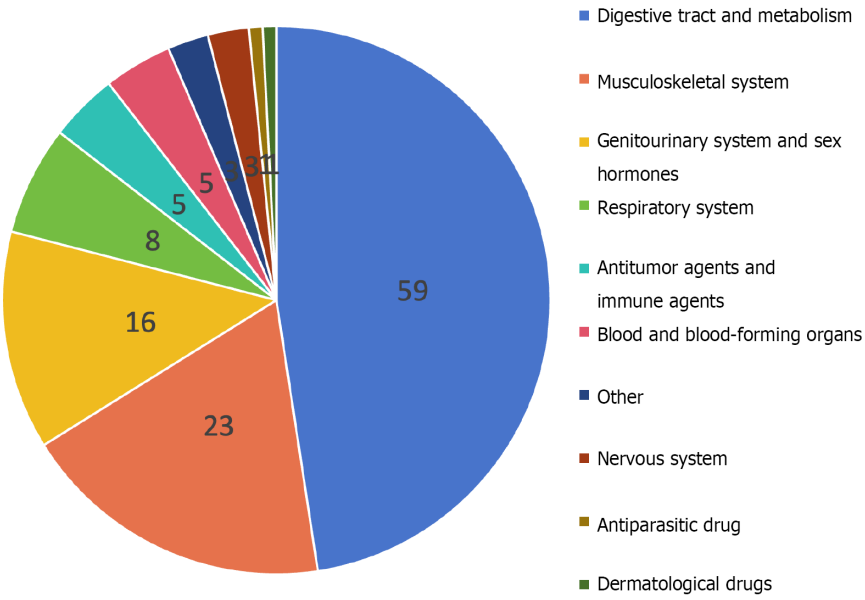

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Figure 7 Anatomic Therapeutic Chemical classification of Chinese patient medicine.

incidence rate and diversity of colon tumors[62]. Traditional Chinese patent medicines and simple preparations containing coix seed was searched on the website of Yaozhi (http://db.yaozh.com/) with the keyword "coix seed". It was recorded in the Ministry of Health drug standard Chinese prescription preparation, China Pharmacopoeia 2020 edition one, Standard for new drug conversion, National standard competition of Chinese patient medicine, New national Chinese patient medicine 2nd edition. There are 134 kinds of traditional Chinese patent medicines and simple preparations containing Coix seed (Figure 5). From the perspective of dosage forms, there are 17 types of traditional Chinese patent medicines and simple preparations containing *Coix lachryma jobi* seed, in which tablets are the main, followed by granules and capsules (Figure 6). We summarized the efficacy of 134 traditional Chinese patent medicines and simple preparations varieties containing coix seed, which can be roughly divided into 9 categories (Figure 7). According to the efficacy analysis, the traditional Chinese patent medicines and simple preparations that contain *Coix lachryma jobi* seed mainly focuses on the digestive system, musculoskeletal system, urogenital system.

Edible value of Coix seed

Coix seed is often used in dietary therapy[25]. Gastrointestinal symptoms caused by chemotherapy, such as weakness, vomiting, and nausea, can be alleviated by qi-yin-reinforcing porridge[63]. In recent years, there have also been many health foods mainly made of Coix seed. The keyword "Coix seed" was searched on Yaozhi.com (http://db.yaozh.com/), and a total of 126 Coix seed related health foods approved by the State Food and Drug Administration were obtained, such as mountain medicine Coix seed granules, Coix seed sea buckthorn capsules, healthy Runtong tea, bone strengthening powder, *etc*, which have immune regulation, weight loss, blood lipid and blood glucose regulation properties. To improve gastrointestinal function and other functions, the statistical data of the health functions involved in Coix Seed Health Products are shown in Figure 8. So far, there are mainly 18 types of Coix seed health product formulations used (Figure 9). The development forms of Coix seed health food functions are very diverse, with diverse products and dosage forms that can meet the specific needs of different populations.

Usage of Coix seed

Coix seed has the effect of promoting metabolism and reducing gastrointestinal burden, and can be used as a nourishing food for weak patients during or after illness[64]. It is worth noting that people with spleen deficiency and diarrhea can stir fry Coix seed before consumption, which has a better effect. Due to its ability to remove dampness, Coix seed should be used with caution for those who suffer from body fluid depletion after fever, or for those who are usually Yin deficient or Yin deficient with excessive fire. Pregnant women and those with slippery semen or constipation should not consume it. If these people consume coix seed, it may cause a greater burden on their physical health.

DISCUSSION

We used Coix Seed; Semen coicis; *Coix lacryma jobi L. var. mayen (Roman.) Stapf* and cancer; neoplasm and tumor as keywords to search on PubMed. And four related reviews were found in the past 5 years. Among them, Huang *et al*[12] discussed the chemical composition, anticancer mechanisms, marketed drugs, dosage forms, and clinical applications of fatty oils, including coix seed and other plants. Pan *et al*[65] only discusses the treatment of malignant tumors in the

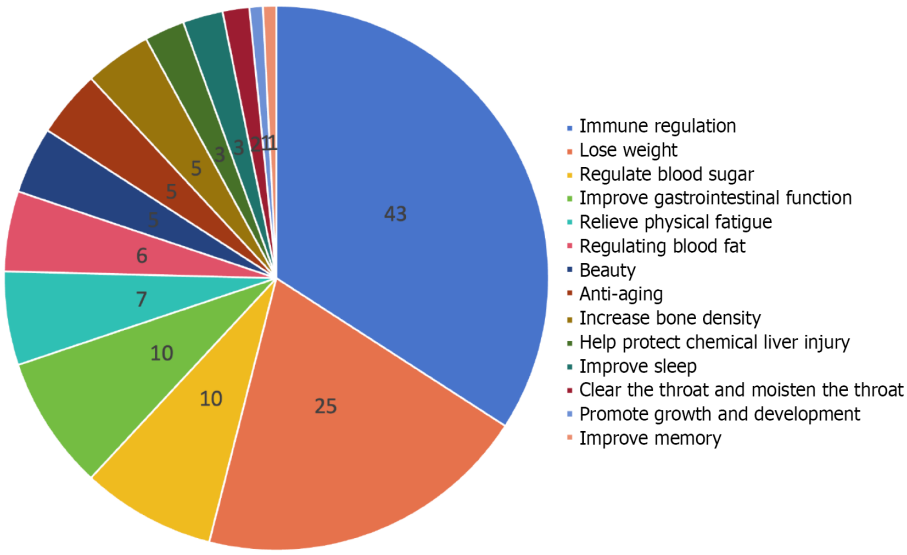

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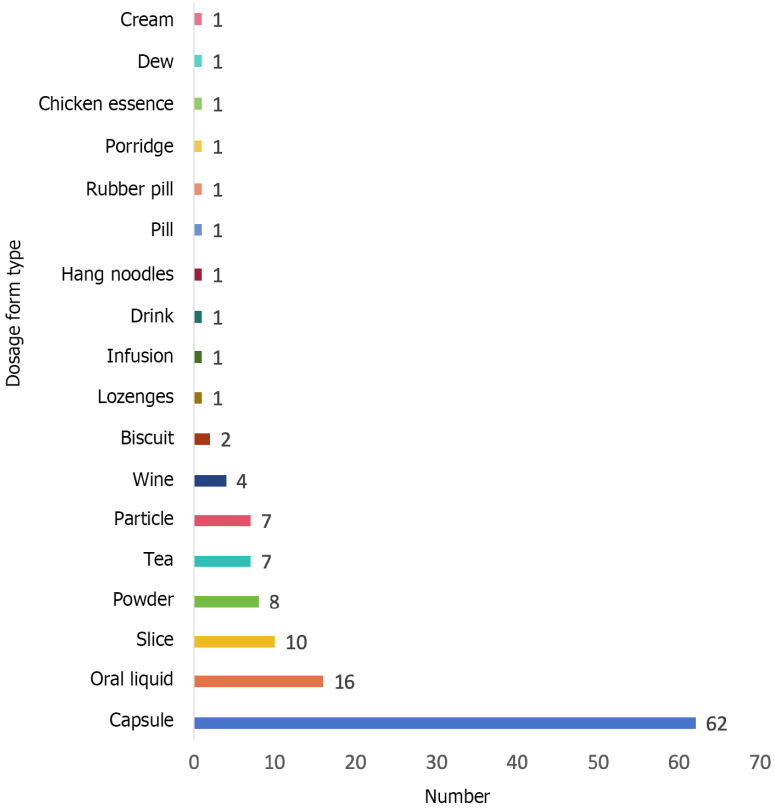
Figure 8 Function statistics of health care products containing Coix seed.



DOI: 10.5306/wjco.v14.i12.593 **Copyright** ©The Author(s) 2023.

Figure 9 Dosage form containing Coix seed health care products.

female reproductive system with coix seed. This article discusses the anti-tumor effect of coix seed and is not limited to malignant tumors in the female reproductive system. Lu *et al*[66] discussed the anticancer effect of KLT, which is an extract of Coix seed oil. This article also discusses some other components of coix seed. Kim *et al*[67] discussed the anti-pancreatic cancer effect of various natural plants including Coix lachryma seed. In the past 5 years, there has been no specialized review on the anticancer effect of Coix seed and its components, as well as the homology between medicine and food. This article starts from the perspective of homology between medicine and food, and conducts KEGG analysis of the effective ingredient targetscoix seed and its components, as well as the homology between medicine and food. This article starts from the perspective of homology between medicine and food, and conducts KEGG analysis of the effective ingredient targets of Coix seed through bioinformatics methods, proving that Coix seed indeed has anti-tumor effects,

and systematically reviews the anti-tumor effect of Coix seed. The application of Coix lachryma seed in traditional Chinese patent medicines and simple preparations and food was also summarized and sorted out, and the relevant data was displayed through charts. Methods, proving that Coix seed indeed has anti-tumor effects, and systematically reviews the anti-tumor effect of Coix seed. The application of Coix lachryma seed in traditional Chinese patent medicines and simple preparations and food was also summarized and sorted out, and the relevant data was displayed through charts.

CONCLUSION

In recent years, more and more studies have shown that Coix seed has the function of inhibiting the growth and metastasis of cancer cells, reducing the mortality rate of cancer patients. Therefore, Coix seed has become a highly anticipated health product. With the increasing emphasis on healthy diet, the idea of "treating diseases before they occur" has become increasingly popular, and Coix seed has received more and more attention in the field of medicinal and food homology. In the future, coix seed can be used to develop various new health products, such as cosmetics, and pharmaceuticals, to meet people's needs for health and beauty. At the same time, Coix seed can also be used to study new medicinal ingredients and treatment methods in order to further improve its health benefits.

FOOTNOTES

Author contributions: Meng FD, Lu DD, Yang YT, Xu DJ, Che MY and Nan Y designed the research study; Meng FD, Yang YT, Che MY and Yuan L collected the literature, Yuan L, Meng FD and Xu DJ analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Clinical outcomes of newly diagnosed primary central nervous system lymphoma treated with zanubrutinib-based combination therapy

Ning Wang, Fei-Li Chen, Lu Pan, Yan Teng, Xiao-Juan Wei, Han-Guo Guo, Xin-Miao Jiang, Ling Huang, Si-Chu Liu, Zhan-Li Liang, Wen-Yu Li

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Abstract

BACKGROUND

High-dose methotrexate (HD-MTX) combined with other chemotherapeutic agents is an effective treatment for patients with newly diagnosed primary central nervous system lymphoma (PCNSL); however, some patients have adverse reactions.

AIM

To retrospectively evaluate disease outcomes and mutational profiles in newly diagnosed PCNSL patients treated with a zanubrutinib/HD-MTX combination regimen.

METHODS

Nineteen newly diagnosed PCNSL patients were treated with zanubrutinib/HD-MTX until disease progression, intolerable toxicities, or physician/patient-directed withdrawal. Safety and efficacy were assessed per the CTCAE v5.0 and RECIST v1.1 criteria, respectively. The primary endpoint was the objective response rate (ORR), and the secondary endpoints were progression-free survival, overall survival (OS), and safety.

RESULTS

The median follow-up duration was 14.7 mo (range, 3.9–30 mo). The ORR for all patients was 84.2%, and 2-year progression-free- and OS rates were 75.6% and 94.1%, respectively. All patients completed the induction phase, and nine patients

underwent autologous stem cell transplantation as consolidation therapy, resulting in an ORR of 88.9%. Ten patients received zanubrutinib as maintenance therapy and achieved an ORR of 80%. All patients showed an acceptable safety profile. The sequencing results for cerebrospinal fluid (CSF) and tumor tissue showed that PIM1 mutations were the most frequent genetic alterations. Circulating tumor DNA was correlated with disease relapse and response.

CONCLUSION

Our empirical observations demonstrated that the combination of zanubrutinib with HD-MTX yielded a marked clinical response and tolerability among newly diagnosed PCNSL patients. Non-invasive CSF liquid biopsy profiling may be feasible for evaluating treatment response and tumor burden.

Key Words: Zanubrutinib; High-dose methotrexate; Primary central nervous system lymphoma; Liquid biopsy; Circulating tumor DNA

Core Tip: Zanubrutinib combined with high-dose methotrexate provided a marked clinical response and tolerance in newly diagnosed primary central nervous system lymphoma patients. Additionally, the detection of circulating tumor DNA in cerebrospinal fluid played a significant part in disease surveillance and treatment response monitoring. However, given the small sample size and retrospective nature of this study, further research is required to validate our findings.

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INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an aggressive lymphoma that is confined to the brain, leptomeninges, eyes, cerebrospinal fluid (CSF), or spinal cord, without evidence of systemic disease[1,2]. Almost all PCNSLs constitute diffuse large B-cell lymphoma (DLBCL)[3]. However, the treatments for PCNSL and DLBCL differ. High-dose methotrexate (HD-MTX) is the primary treatment for PCNSL. HD-MTX (3.5 g/m^2) combined with other chemotherapeutic agents is effective; however, some patients have adverse reactions[4,5]. Therefore, it is necessary to identify drugs that can be combined with HD-MTX to solve this issue.

Zanubrutinib, a novel oral inhibitor of Bruton's tyrosine kinase (BTK), is a promising therapeutic intervention in B-cell antigen receptor (BCR) and Toll-like receptor (TLR) signaling. This signaling network integrates signals from the BCR and TLR pathways. The key players, BCR-associated protein CD79B and myeloid differentiation primary response 88 (MYD88), act as bridges linking interleukin-1 and TLRs with the potent nuclear factor kappa B pathway[6-9]. Activating mutations were observed in MYD88 and CD79B across various studies of PCNSL[6,10-13]. Studies have shown that BTK inhibitors can cross the blood-brain barrier and effectively modulate signaling cascades downstream of MYD88 and CD79B[14-17], demonstrating their potential efficacy in PCNSL. Recent studies on zanubrutinib-containing therapeutic regimens have highlighted their effectiveness in cases of DLBCL with CNS involvement[18]. However, despite these advancements, a critical gap remains: the absence of concrete clinical evidence supporting the use of zanubrutinib in PCNSL with CNS involvement. The BTK inhibitor, ibrutinib, combined with HD-MTX has demonstrated an objective response rate (ORR) of 80% with an acceptable safety profile in a phase Ib study[19]. Therefore, we retrospectively analyzed the clinicopathological characteristics, treatment outcomes, and adverse events in newly diagnosed PCNSL patients treated with combined HD-MTX and zanubrutinib. We also explored the next-generation sequencing of circulating tumor DNA (ctDNA) in CSF, both before and during treatment, as well as the safety profile, treatment response, and genomic biomarkers.

MATERIALS AND METHODS

Patients

From May 2020 to April 2022, 19 eligible PCNSL patients from XX Hospital, China, were identified for inclusion in this study. The inclusion criteria were as follows: (1) Newly diagnosed pathologically confirmed PCNSL; (2) ≥ 18 years of age; (3) Treatment with HD-MTX and zanubrutinib combination therapy; and (4) Received at least two cycles of chemotherapy. The exclusion criteria were as follows: (1) Non-primary CNS lymphoma; (2) Previous treatment with other BTK

inhibitors; and (3) Patients with incomplete follow-up data, for whom we were unable to evaluate efficacy. The selection criteria are also shown in Figure 1.

This study was approved by the Clinical and Research Ethics Committee of the Guangdong Provincial People's Hospital, Guangzhou, China. All procedures in the present study that involved human participants were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in this study.

Treatment protocol

The treatment regimen was designed to achieve optimal outcomes through induction therapy with combined HD-MTX and zanubrutinib. HD-MTX was administered at a dose of 3.5 g/m^2, with a total of 4-8 doses planned. Zanubrutinib was prescribed at a dose of 160 mg orally (PO) twice daily (BID). Zanubrutinib administration was paused on the days of HD-MTX infusion to mitigate potential interactions and was resumed once HD-MTX clearance was achieved. Following induction therapy, zanubrutinib was administered as maintenance therapy until specific endpoints were reached, namely disease progression, intolerable toxicity, autologous stem cell transplantation (ASCT), or mortality.

Stem cell assessment and ASCT

Prior to ASCT, a comprehensive evaluation of each patient's stem cell composition was performed. The ASCT process comprised the use of peripheral blood autologous hematopoietic stem cells. To prepare patients for ASCT, a pre-conditioning regimen was administered that comprised either carmustine, etoposide, cytarabine, and melphalan or carmustine, etoposide, cytarabine, and cyclophosphamide. This pre-conditioning aimed to optimize the transplantation environment. Subsequently, granulocyte colony-stimulating factor was administered to mobilize stem cells. The screening process involved monitoring cluster of differentiation 34-positive (CD34+) hematopoietic stem cells in peripheral blood using flow cytometry. The ideal threshold for peripheral blood CD34+ cells was set at ≥ 20 cells/μL. This monitoring enabled prediction of the required collection quantity and duration, with a minimum standard of CD34+ cells not at 2 × 10^6/kg. A desirable transplant condition was generally achieved when the final collection of CD34+ cells exceeded 5 × 10^6/kg.

Response assessment

Therapeutic response was evaluated in accordance with the international PCNSL Collaborative Group guidelines[1]. Response to treatment was assessed using magnetic resonance imaging and CSF evaluation every second cycle. In accordance with the guidelines, each patient's best response to treatment was recorded to evaluate the ORR, including complete response (CR, no contrast enhancement on imaging) and partial response (≥ 50% decrease disease enhancement on imaging). Any new lesions were defined as progressive disease (PD), and any other conditions were defined as stable disease. Progression-free survival (PFS) was calculated from the start of treatment to the time of disease progression or death due to PCNSL. Overall survival (OS) was calculated from the date of diagnosis to the time of death from any cause.

Sample collection and processing

CSF and peripheral blood samples were collected and stored at -80°C. Tumor biopsy specimens were obtained using formalin-fixed, paraffin-embedded tissues. Samples were analyzed using capture-based targeted next-generation sequencing in a central testing laboratory (Nanjing Geneseq Technology, Inc., Nanjing, China). This approach, as previously outlined, targets 102 lymphoma-associated genes, facilitating precise genetic characterization[20,21]. The DLBCL [non-germinal center B-cell (non-GCB) or germinal center B-cell (GCB)] subtype was determined using immuno-histochemical staining in accordance with the Hans classification, in the Department of Pathology of the Guangdong People's Hospital, Guangzhou, China.

Statistical analysis

GraphPad Prism 9 (version 9.0.2; GraphPad Software, Inc., San Diego, CA, United States) was used for the data analysis. Baseline characteristics were described using medians for continuous variables and percentages for categorical variables. PFS and OS were analyzed by the Kaplan–Meier method, P values were calculated using the log-rank test, and $P < 0.05$ indicated a significant difference.

RESULTS

Baseline patients' data

Data for 19 patients with newly diagnosed PCNSL who were treated with HD-MTX plus zanubrutinib were retrospectively analyzed (Figure 1). The patients' clinicopathological characteristics are summarized in Table 1. The patients' median age was 57 years (range, 27-81 years), and five patients had an Eastern Cooperative Oncology Group performance score > 2 (Table 1). Ten patients were women, and 16 patients had lesions in deep areas, namely the periventricular tissue, corpus callosum, brainstem, basal ganglia, and/or cerebellum. Eleven patients had high CSF protein concentrations (> 450 mg/L), and only one patient had a high lactate dehydrogenase serum level (> 250 U/L). The International Extranodal Lymphoma Study Group risk score was low-grade in 3 patients, median-grade in 12 patients, and high-grade in 1 patient.

Table 1 Baseline data of the patients with primary central nervous system lymphoma

Characteristic	*N* = 19
Age, yr	57 (27–81)
Sex, *n* (%)	
Male	9 (47.4)
Female	10 (52.6)
ECOG-PS ≥ 2, *n* (%)	5 (26.3)
Invasion of deep intracranial areas, *n* (%)	16 (84.2)
High CSF protein concentration (> 450 mg/L), *n* (%)	11 (68.75)[1]
High LDH serum concentration (> 250 U/L), *n* (%)	1 (5.3)
IELSG risk score, *n* (%)	
Low	3 (18.75)[1]
Intermediate	12 (75)[1]
High	1 (6.25)[1]
Follow-up time (mo)	14.7 (3.9–30)

[1]Three patients refused lumbar puncture for personal reasons.
ECOG-PS: Eastern Cooperative Oncology Group performance score; CSF: Cerebrospinal fluid; LDH: Lactate dehydrogenase; IELSG: International Extranodal Lymphoma Study Group.

Treatment duration and response

All 19 patients received 120 doses of induction therapy. ASCT was administered as consolidation therapy in nine patients. None of the patients received corticosteroid therapy. HD-MTX therapy was discontinued in one patient due to delayed HD-MTX excretion. Nine patients completed ASCT, with an ORR of 88.9% (CR/PR: 6/2). Eight patients were still in remission at the time of writing (Figure 2 and Table 2). Ten patients received maintenance therapy comprising zanubrutinib with lenalidomide for 6 mo, and zanubrutinib monotherapy was administered continuously until disease progression.

The median follow-up duration was 14.7 mo (range, 3.9-30 mo). All patients were evaluated for treatment response, which revealed CR in 11 patients, partial response in 5 patients, and PD in 3 patients. The ORR was 84.2%, and 2-year PFS and OS rates were 75.6% and 94.1%, respectively. The median PFS and median OS for the entire cohort were not reached (Table 3 and Figure 3).

Safety and adverse events

The prevalent hematological toxicity in patients who received HD-MTX plus zanubrutinib treatment was anemia (100%), followed by lymphocytopenia (84.2%). The leading non-hematological toxicities were hypoalbuminemia (94.7%) and hypokalemia (78.9%) (Table 4). It is noteworthy that no grade 4 non-hematological toxicities were recorded, and the observed adverse effects of therapy were mild and required no additional therapeutic interventions. No treatment-related fatalities were observed.

Clinical response and baseline tumor genomic characteristics

We also explored the association between treatment response and tumor genomic traits. CSF samples were available for eight patients, while six patients had baseline tumor biopsy samples available for genomic analysis (Figure 4). Forty-two genetic alterations were detected (tumor tissue samples: n = 30, CSF samples: n = 30), and 18 alterations were the same in the primary tumor tissue and CSF samples (Figure 5). The most common mutation detected in both CSF and primary tumor samples was PIM1, followed by alterations of B-cell lymphoma 6, MYD88, GNA13, and TBL1XR1.

Among the 19 patients, 9 had non-GCB disease, with 6 (66.7%) responding positively to the zanubrutinib-based regimen. The remaining 10 patients with GCB disease achieved a 100% response rate to the same regimen. Among the patients with MYD88 alterations, four achieved CR, constituting 50% of this subgroup, with the zanubrutinib-based regimen. In the subset of eight patients with alterations in key genes involved in the BCR pathway, such as CD79B and MYD88, the ORR reached 60%. The response rates for patients with alterations in MYD88 and CD79B were 50% (4/8) and 37.5% (3/8), respectively (Table 2). Two patients (P1 and P7) with alterations in both MYD88 and CD79B genes demonstrated a 50% ORR, with one achieving a CR, as shown in Table 2.

The role of CSF ctDNA in disease surveillance

Eight CSF samples were collected during various treatment cycles, *i.e.*, at baseline and just before cycles 3, 5, and 6. One exception was patient 6, who underwent assessments only after cycle 3 and cycle 6 for personal reasons. Six patients

Table 2 Baseline tumor genomic characteristics of the patients with primary central nervous system lymphoma

Patient	ID	COO Subtype	Best response (mo)	MYDBB	CD79B	Ki-67	Cyclin D1	Other IHC results
p973624	1	Non-GCB	CR (22.2)[1]	L265P	Y196D	> 90%+	NA	CD20(+++), CD79a(+++), CD3(−), CD5(−), CD21(−), CD23(−), Bcl6(>90%+), MUM1(>90%+), FOXP1(>90%+), Bcl2(60%+), c-Myc(40%+), CD30(−), ALK(ALK1)(−), CD138(−), P53(+), c-Met(−), PD-L1(22C3)(30%+)
p968283	2	GCB	CR (23)[1]	NA	NA	100%+	−	CD43(−), CD20(+++), CD3(−), CD79a(+++), CD5(−), CD23(−), CD10(95%+), CD21(−), CD30(−), ALK(ALK1)(−), Bcl6(90%+), CD138(−), MUM1(65%+), Bcl2(50%+), c-Myc(20%+), GFAP(−), Olig2(−)
p955842	3	Non-GCB	SD (6.0)	NA	NA	70%+	−	LCA(+++), OCT-2(+++), CD20(+++), CD19(+++), CD10(−), Bcl6(70%+), MUM1(40%+), CD3(−), CD5(+), ALK(ALK1)(-), CD23(−), CD21(−), CD30(−), CD138(−), Bcl2(++), TdT(−), GECT1(+), FOXP1(+++), c-Myc(80%+), c-Met(−), P53(+++), GFAP(−), CK(−), EMA(−)
p241574	4	Non-GCB	CR (27.5)[1]	NA	K159Q, V223R	90%+	−	LCA(++), CD79a(++), CD43(−), CD20(+), CD3(−), CD5(−), CD23(−), CD10(−), CD21(−), CD30(−), ALK(ALK1)(−), Bcl6(90%++), CD138(−), MUM1(70%+), Bcl2(50%+), TdT(−), GECT1(30%+), FOXP1(+), c-Myc(70%+), c-Met(+), LMP-1(−), EBNA2(−), P53(+), PD-L1(22C3)(90%+)
p939668	5	Non-GCB	PR (28.5)[1]	NA	NA	NA	NA	NA
p932230	6	GCB	CR (29.5)[1]	S219C	NA	98%+	NA	CD20(+++), CD79a(+++), CD3(−), CD5(−), ALK(ALK1)(−), CD21(−), CD23(−), Bcl6(90%+), MUM1(20%+), CD10(100%+), CK(−), Vimentin(−), EMA(−), S100(−), GFAP(−), Bcl2(80%+), GECT1(35%+), FOXP1(80%+), c-Myc(45%+), C-MET(50%+), P53(4%+), PD-L1(22C3)(10%+)
p929763	7	Non-GCB	CR (18.8)	L265P	C.553-2A>C	90%+	−	CD43(−), CD20(+++), CD3(−), CD79a(+++), CD5(−), CD23(−), CD10(−), CD19(+++), CD22(++), CD21(−), CD30(−), ALK(ALK1)(−), Bcl6(10%+), CD138(−), MUM1(20%+), Bcl2(70%+), TdT(−), c-Myc(5%+), GFAP(−)
p173185	8	Non-GCB	PR (8.0)	L265P	NA	NA	NA	ERCC1(−), β-tubulin(+++), EGFR(+++), VEGF(+), ALK(−), CD56(−), CgA(−), Syn(−)
p651739	9	GCB	CR (23.0)	NA	NA	90%+	−	CD43(+), CD20(+++), CD3(+), CD79a(++), CD5(−), CD23(−), CD10(+++), CD21(−), CD30(−), ALK(ALK1)(−), Bcl6(60%+), CD138(−), MUM1(++), Bcl2(−), TdT(−), c-Myc(20%+), GFAP(−), Olig2(−)
p1013138	10	GCB	CR (12.5)	NA	NA	90%+	−	CD3(−), CD5(−), CD20(++), CD79a(++), CD30(−), ALK(ALK1)(−), SALL4(−), OCT3/4(−), AFP(−), GFAP(−), Olig2(−), MUM1(+), CD10(++), Bcl6(++), CD23(−), Bcl2(−), GCET-1(+), FOXP1(+), c-Myc(70%+), c-Met(−), P53(95%++), PD-L1(22C3)(TC <1%+, IC 70%+)
p2010722	11	Non-GCB	PR (16.6)	NA	NA	80%+	−	CK(−), CD20 and CD79a(+), CD3(−), CD5(−), Bcl-2(80%+),

								MUM-1(+), CD10(−), Bcl6(−)
p998505	12	Non-GCB	PR (22.2)	NA	NA	70%+	2%+	D3(+), CD5(++), CD20(+++), CD79a(+++), CD30(−), CD10(−), GFAP(−), Olig2(−), CK(−), CD43(++), CD23(−), CD21(−), ALK(ALK1)(−), Bcl6(20%+), CD138(−), MUM1(80%+), Bcl2(90%+++), TdT(−), GCET-1(−), FOXP1(+++), c-Myc(70%+), c-Met(−), P53(1%+), PD-L1(22C3)(70%+)
p1013897	13	GCB	CR (14.2)	NA	NA	85%+	−	CD20(+++), CD3(−), CD79a(+++), CD5(−), CD30(<1%+), ALK(ALK1)(−), CD23(−), CD10(+++), CD21(−), Bcl6(70%+), CD138(+), MUM1(40%+), Bcl2(5%+), TdT(−), Cyclin D1(−), c-Myc(40%+), c-Met(60%+), P53(70%+), PD-L1(22C3)(40%+)
p2020811	14	GCB	CR (10.8)	NA	NA	90%+	NA	CD3(+), CD5(+), CD79a(+), CD10(+), Bcl6(±), CD20(+++), Bcl6(80%+), MUM1(<5%+), CD10(+), Ki67(90%+), CD3(−), AE1/AE3(−), EMA(−), P40(−), CD3(−), GFAP(−)
P2003851	15	GCB	CR (13.1)	NA	NA	80%+	−	EMA(−), S100(−), GFAP(+), Syn(+), CgA(−), Olig2(+), NeuN(+), CD34(+), CD3(+), CD5(+), CD79a(+), CD20(+), CD43(10%+), CD30(−), ALK(ALK1)(−), Bcl6(>90%+), Bcl2(90%+), TdT(−), GCET-1(90%+), FOXP1(>90%+), c-Myc(40%+), c-Met(−), LMP-1(−), EBNA2(−), P53(60%+), PD(−), L1(22C3)(30%+)
p996213	16	GCB	CR (18.3)	NA	NA	NA	NA	NA
P1010986	17	GCB	CR (14.7)	NA	NA	95%+	−	CD43(+), CD20(+++), CD3(−), CD79a(++), CD5(−), CD23(−), CD10(60%+), CD21(−), CD30(−), ALK(ALK1)(−), Bcl6(60%+), CD138(−), MUM1(90%+), Bcl2(15%+), TdT(−), c-Myc(30%+)
P2052819	18	Non-GCB	PR (3.9)	NA	NA	90%+	−	GFAP(−), Olig2(−), CD20(+++), CD79a(++), CD3(−), CD5(−), CD21(−), CD23(−), CD10(−), Bcl6(60%++), MUM1(90%+++), CD138(−), Bcl2(90%+++), c-Myc(70%++), CD30(−), ALK(ALK1)(−)
P2045773	19	GCB	PR (5.2)	NA	NA	90%+	−	CD19(+++), CD20(+++), CD3(−), CD5(−), GFAP(−), Olig2(−), CD23(+), CD10(−), CD21(−), CD30(−), ALK(ALK1)(−), Bcl6(70%+), CD138(−), MUM1(70%+), Bcl-2(95%+), TdT(−), c-Myc(40%+), c-Met(−)

[1]Still in remission.

PCNSL: Primary central nervous system lymphoma; ID: Identification number; COO: Cell of origin; NA: Not available; IHC: Immunohistochemistry; GCB: Germinal center B cell; CR: Complete response; SD: Stable disease; PR: Partial response: CD: Cluster of differentiation; Bcl6: B cell lymphoma 6; MUM-1: Multiple myeloma antigen 1; FOXP1: Forkhead box protein P1; Bcl2: B cell lymphoma 2; ALK: Anaplastic lymphoma kinase; PD-L1: Programmed death-ligand 1; GFAP: Glial fibrillary acidic protein; LCA: Leucocyte common antigen; TdT: Terminal deoxynucleotidyl transferase; GECT: Gene expression in developing tissues with micro computed tomography; CK: Cytokeratin; EMA: Epithelial membrane antigen; LMP-1: Epstein–Barr virus-encoded latent membrane protein 1; EBNA2: Epstein–Barr virus nuclear antigen 2; P53: Tumor protein 53; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; CgA: Chromogranin A; Syn: Syndecan; SALL4: Sal-like protein 4; AFP: Alpha fetoprotein; Olig2: Oligodendrocyte lineage transcription factor 2; TC: Tumor cells; IC: Immune cells; D3: Cyclin D3; NeuN: Neuronal nuclear antigen.

showed a robust radiographic response to treatment, resulting in a significant reduction in CSF mutant allele frequency. One patient (P3) showed a stable radiographic response, confirmed by magnetic resonance imaging, but the ctDNA levels remained unchanged in the CSF specimen (Figure 6). However, this patient experienced PD following completion of the zanubrutinib-based induction regimen. Therefore, whole-brain radiotherapy (30 GY) with temozolomide and zanubrutinib was initiated. This approach led to a favorable radiographic response, and the patient is presently

Table 3 Efficacy of high-dose methotrexate plus zanubrutinib for newly diagnosed primary central nervous system lymphoma

Parameter	*N* = 19
OS rate (%)	-
24-mo (95%CI)	94.1% (83.6%-100%)
Median PFS	-
24-mo (95%CI)	75.6% (53.4%-100%)
ORR (%)	84.2%
ASCT (consolidation therapy)	88.9%
Zanubrutinib (maintenance therapy)	80%
Median follow-up time (mo)	14.7
95%CI	3.9–30

OS: Overall survival; CI: Confidence interval; PFS: Progression-free survival; ORR: Objective response rate; ASCT: Autologous stem cell transplantation.

Table 4 Adverse events in patients treated with high-dose methotrexate plus zanubrutinib

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
Hematological toxicities					
Leukopenia	3	7	1		11 (57.9)
Neutropenia	3	6	2		11 (57.9)
Lymphocytopenia	6	8	2		16 (84.2)
Thrombocytopenia	5			1	6 (31.6)
Anemia	8	10	1		19 (100)
Non-hematological toxicities					
Transaminase increase	4				4 (21.1)
Creatinine increase	2	1			3 (15.8)
Hypoalbuminemia	16	2			18 (94.7)
Hypokalemia	10	4	1		15 (78.9)
Lung infection					NA

NA: Not applicable.

continuing with this treatment. Another patient (P8) demonstrated a partial radiographic response. The mutant allele frequency in the CSF decreased markedly with treatment, excluding the gene fusion of BCR-ABL1 (Figure 6). However, this patient developed PD as peripheral lesions, and subsequently received rituximab, zanubrutinib, and lenalidomide (IR2) as second-line treatment.

DISCUSSION

The outcomes in our case series showed that combined therapy with zanubrutinib and HD-MTX was well-tolerated as a frontline therapeutic regimen for patients diagnosed with PCNSL. Nine patients transitioned to ASCT following the zanubrutinib and HD-MTX induction phase, while another 10 patients underwent maintenance therapy with zanubrutinib alone. Only three patients developed disease progression. Data for all 19 patients were included in the evaluation of PFS and OS. Only one patient (P6) discontinued HD-MTX therapy, owing to delayed HD-MTX excretion, and the regimen was changed to rituximab, zanubrutinib, and lenalidomide. No instances of treatment-related mortality were recorded throughout the study. However, limitations exist in our study. It is well recognized that the journey from the initiation of the oncogenic event to the point of clinical diagnosis is protracted, spanning approximately a decade. This extended timeline underscores the intricacies inherent in the development of neoplastic disorders, revealing that the characterization of "newly diagnosed" necessitates a more nuanced understanding-one that acknowledges the substantial

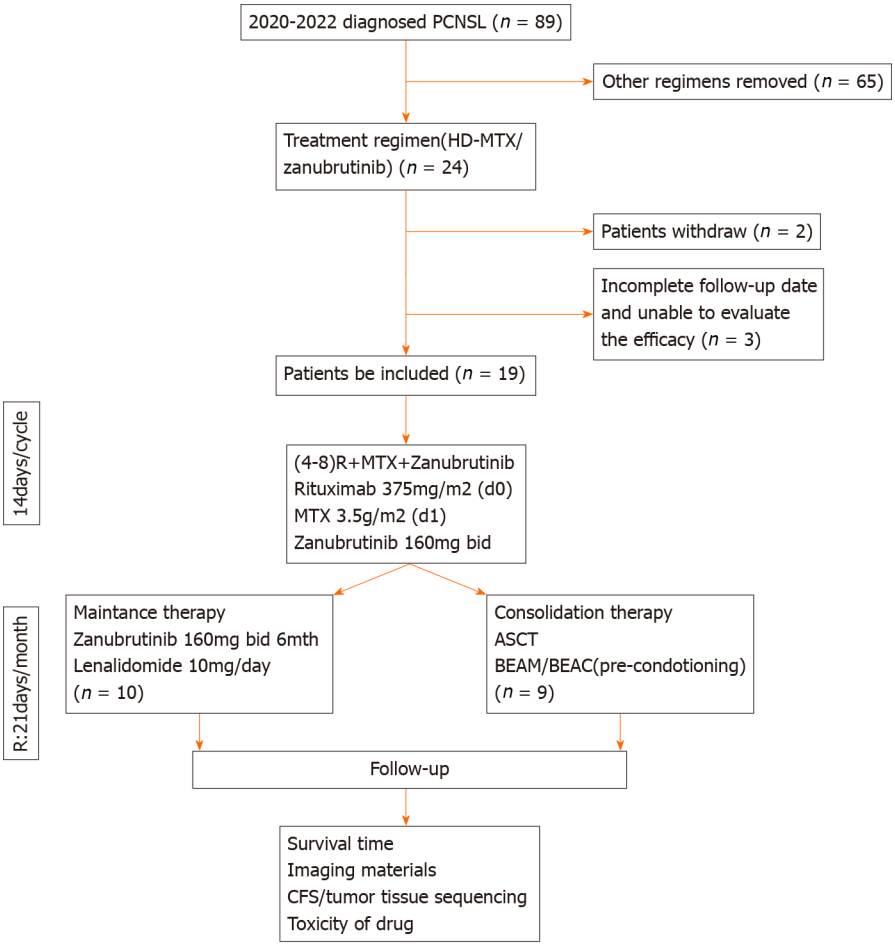

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Figure 1 Patient acquisition flow diagram. PCNSL: Primary central nervous system lymphoma; HD-MTX: High-dose methotrexate; ASCT: Autologous stem cell transplantation; BEAM: Carmustine, etoposide, cytarabine, and melphalan; BEAC: Carmustine, etoposide, cytarabine, and cyclophosphamide; CFS: Cancer Fatigue Scale. R:21 days/month: Lenalidomide for maintenance therapy.

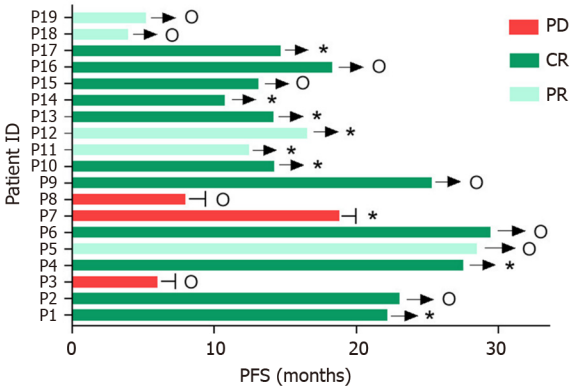

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Figure 2 Clinical response and progression-free survival of all patients. o: using a zanubrutinib-based maintenance regimen. ∗: Using ASCT as a consolidation regimen; →: Ongoing; ⊣: PD; ID: Identification number; PD: Progressive disease; CR: Complete response; PR: Partial response; PFS: Progression-free survival; ASCT: Autologous stem cell transplantation.

span of disease evolution prior to medical recognition.

Our study emphasizes the importance of adopting novel therapeutic strategies to address the multifaceted nature of PCNSL. Historically, HD-MTX has played a pivotal role, serving as a cornerstone for first-line induction regimens in PCNSL. This is owing to its ability to penetrate the blood-brain barrier and achieve effective anti-tumor concentrations [22-24]. However, even with this treatment, approximately half of the patients experience relapse, and 5-year survival rates remain discouragingly low, at 30%-40%[3]. Studies have shown that HD-MTX-based first-line regimens result in an

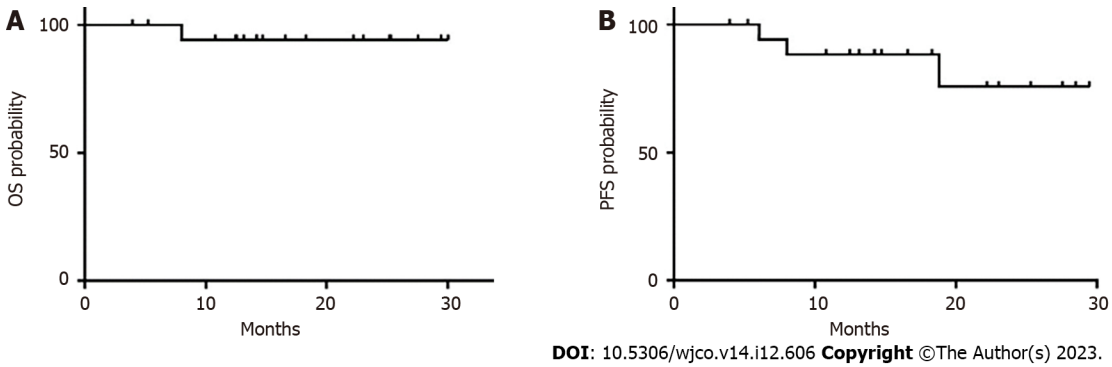

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Figure 3 Kaplan-Meier curve for overall survival and progression-free survival. A: overall survival; B: progression-free survival. OS: Overall survival; PFS: Progression-free survival.

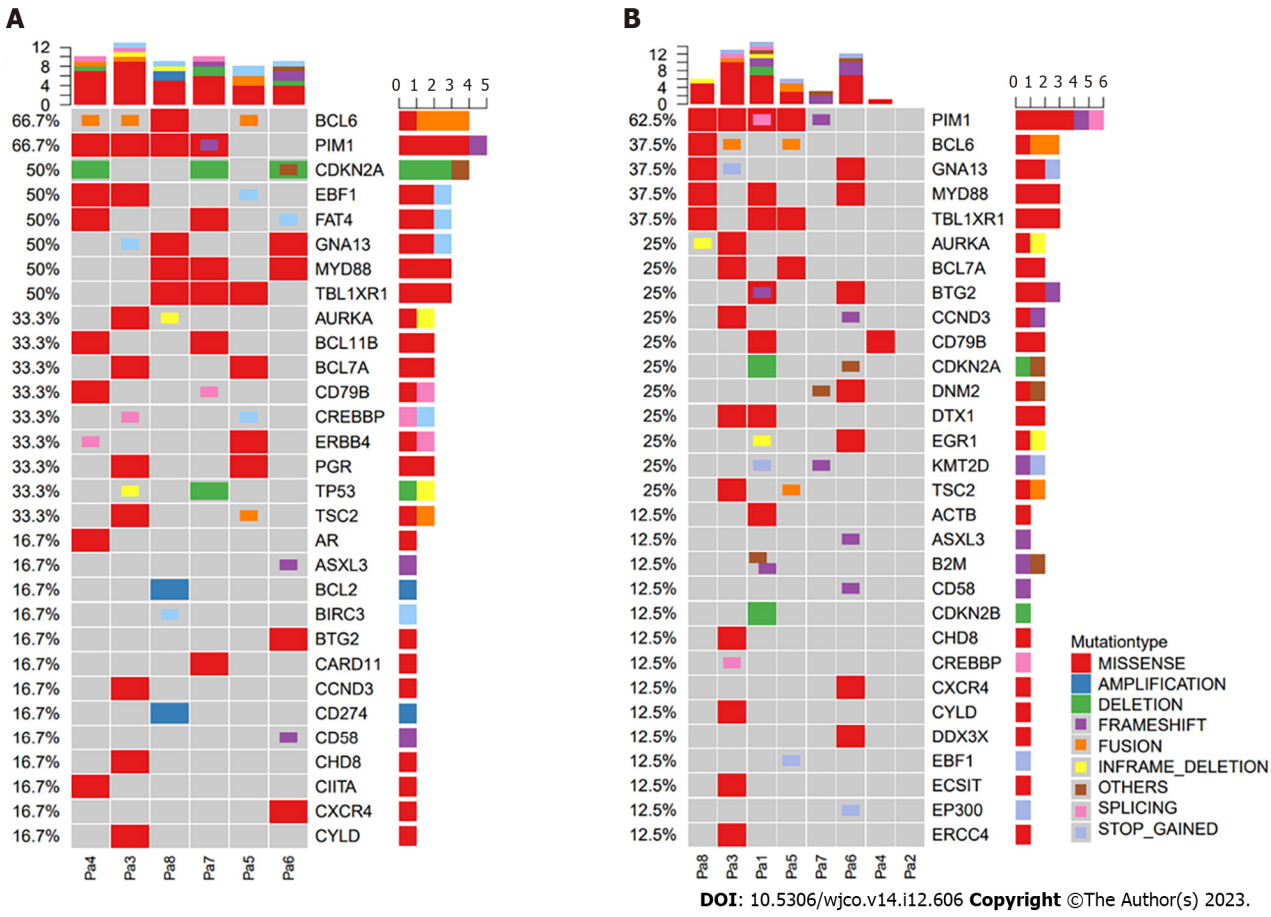

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Figure 4 Gene alterations detected in tumor tissue and cerebrospinal fluid. A: Tumor tissue; B: Cerebrospinal fluid. CSF: Cerebrospinal fluid; P: Patient.

ORR of approximately 68% in PCNSL patients over the age of 60 years. In newly diagnosed PCNSL, the median PFS is 35 mo and 8 mo for patients younger and older than 60 years, respectively[22,25]. In this study, the combination of zanubrutinib with HD-MTX demonstrated robust anti-tumor activity, with an ORR of 84.2%, which is higher than that achieved by HD-MTX-based chemotherapy alone. Our results also identified a 2-year PFS of 75.6% and an OS of 94.1%. The median PFS and median OS for the entire cohort were not reached at the time of writing, even after a follow-up of 14.7 mo (range: 3.9-30 mo). Previous studies have shown that zanubrutinib exhibits greater selectivity in inhibiting BTK compared with the off-target effects observed with ibrutinib[26]. The profound BTK inhibition observed with zanubrutinib in both blood and lymph nodes is hypothesized to maximize the potential for deep and sustained remissions in conditions such as chronic lymphocytic leukemia and other hematological disorders. In the phase I BGB-3111-AU-003 study, which evaluated zanubrutinib monotherapy for chronic lymphocytic leukemia/small lymphocytic leukemia, efficacy was assessed in a cohort of 78 patients. This patient group included individuals with high-risk disease features, such as adverse cytogenetics (del(11q), 23.3%; del(17p) and/or TP53 mutation) at a rate of 19.1%[26]. After a

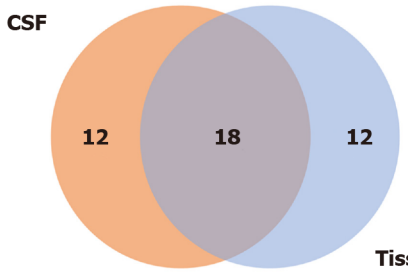

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Figure 5 Concordance between baseline primary tumor tissue and cerebrospinal fluid samples for mutation detection. CSF: Cerebrospinal fluid.

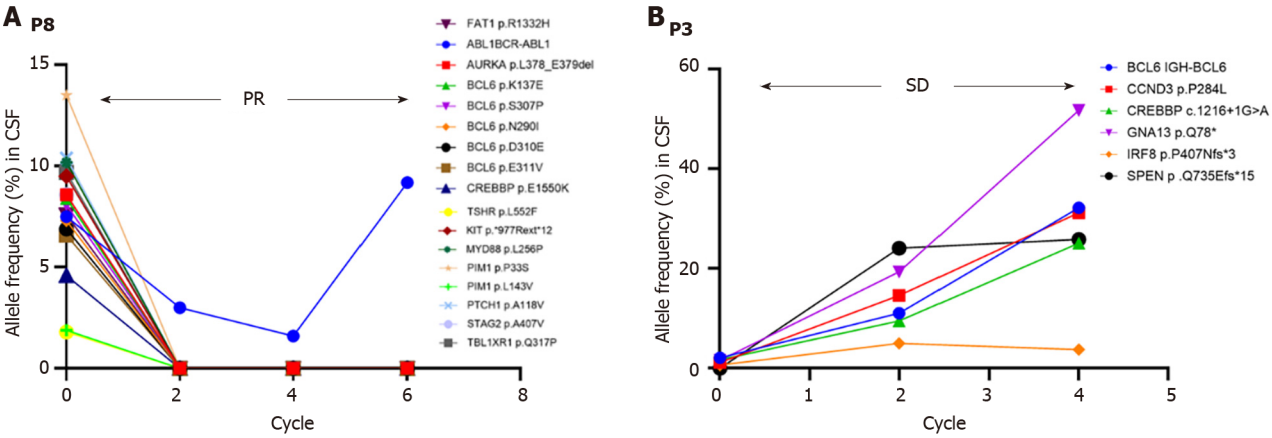

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Figure 6 Disease monitoring during therapy by evaluating cerebrospinal fluid circulating tumor DNA. A: P8; B: P3. PR: Partial response; SD: Stable disease; P8: Patient 8; P3: Patient 3.

median follow-up of 13.7 mo (range: 0.4-30.5 mo), the ORR was 96.2% (75/78) (95% confidence interval: 89.2-99.2). This ORR group included two patients (2.6%) who achieved CR, 63 (80.8%) who achieved PR, and 10 (12.8%) with PR with lymphocytosis[26].

In our study, nine patients completed ASCT after the induction phase of zanubrutinib-based combination therapy and achieved an ORR of 88.9% (CR/PR: 6/2), indicating the advantage of ASCT as a consolidation regimen. Furthermore, studies have shown that ASCT is an effective consolidation strategy in PCNSL[27,28]. Therefore, ASCT should be the first choice for suitable patients.

Lenalidomide is an immunomodulatory agent that shows good anti-tumor activity as a BTK inhibitor in DLBCL[27]. Lenalidomide combined with ibrutinib and rituximab shows promising anti-tumor activity in relapsed/refractory DLBCL[29]. In our study, one patient (P6) achieved CR after receiving an IR2-based regimen and zanubrutinib maintenance. In patients who do not tolerate HD-MTX and experience toxicity, IR2 may be a better choice. In our study, 8 of 10 patients achieved a therapeutic response with zanubrutinib maintenance. Therefore, for PCNSL patients who are unsuitable for ASCT, lenalidomide and zanubrutinib as maintenance therapy might be promising.

PCNSL patients are divided into three major molecular subtypes: A GCB subtype, an activated B-cell (ABC) subtype, and a type III subtype, whose cell origin is unidentified. The first two subtypes account for approximately 80% of all cases; ABC DLBCL patients have poorer outcomes[30]. To our knowledge, there are no reports of the results of zanubrutinib therapy for the GCB and ABC subtypes of PCNSL. Nine of the 19 patients in our study had non-GCB disease and 6 (66.7%) responded to the zanubrutinib-based regimen. Ten patients had GCB disease, and all (100%) responded to the zanubrutinib-based regimen. Zanubrutinib may have had a better effect on the ABC subtype in previous studies.

Previous studies have shown that next-generation sequencing may be used as a molecular diagnostic method prior to delivering targeted therapies, particularly BCR inhibitors, in the case of MYD88-mutated tumors[31]. In our study, CSF liquid biopsies were evaluated using next-generation sequencing in eight patients, while XX underwent radiological evaluation. Six patients had dramatically lower CSF mutant allele frequencies compared with patients 3 and 8. Patient 8 achieved a partial radiographic response during the induction treatment, while the CSF mutant allele frequency increased after cycle 4 (Figure 6). This patient developed PD while receiving the maintenance regimen. As shown in Figure 6, patient 3 had a stable radiographic response, with an increased level of ctDNA in the CSF specimen. This patient developed PD after completing the induction regimen.

Performing CSF liquid biopsy profiling with radiologic evaluation is feasible in PCNSL. Studies show frequent MYD88 and CD79B mutations in PCNSL[6,10-13]. On the basis of the genetic analysis of CSF in our study, we found frequent alterations of MYD88 and CD79B involved in the BCR pathway, and zanubrutinib combined with HD-MTX resulted in good anti-tumor activity. Therefore, CSF liquid biopsy profiling might be feasible for evaluating the response to a therapeutic protocol. However, the fleeting presence of ctDNA in the bloodstream poses a challenge to the reliability of the results of CSF liquid biopsy profiling[32].

An extensive safety analysis performed on pooled data from six zanubrutinib monotherapy trials revealed a notable trend toward favorable tolerability among patients diagnosed with various B-cell malignancies[29]. These conditions, which are often associated with symptoms such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, skin rash, and fatigue, respond well to zanubrutinib treatment[33]. The results of our study highlight the reassuring absence of grade 4 non-hematological toxicities. The reported side effects were characterized as mild and did not require further therapeutic intervention. No treatment-related mortality was observed, indicating a moderate safety profile for zanubrutinib combined with HD-MTX for patients with PCNSL.

While our findings provide valuable insights into the tolerability of zanubrutinib, this study has limitations. First, owing to the retrospective design and the small number of included patients, larger-scale prospective cohort studies and longer follow-up may be warranted to validate our results. Second, generally, regarding cellular origin in PCNSL, zanubrutinib may have a better effect on the ABC subtype. However, in this study, we were able to identify only the GCB and non-GCB phenotypes owing to the limited experimental conditions; ABC genotyping was not performed. Therefore, it is not possible to conduct a more detailed analysis.

CONCLUSION

Zanubrutinib combined with HD-MTX provided a good clinical response and was well tolerated in newly diagnosed PCNSL patients. Additionally, the detection of ctDNA in CSF was very useful in disease surveillance and treatment response monitoring. However, given the small sample size and retrospective study design, further research is required to validate our findings.

ARTICLE HIGHLIGHTS

Research background

Primary central nervous system lymphoma (PCNSL) is an aggressive brain lymphoma with limited treatment options. The current standard treatment involves high-dose methotrexate (HD-MTX), but there is a need for effective combination therapies to address adverse reactions. Zanubrutinib, a Bruton's tyrosine kinase inhibitor, shows promise owing to its potential to modulate B-cell receptor and Toll-like receptor signaling, which are associated with PCNSL.

Research motivation

This study aimed to evaluate the efficacy and safety of combining zanubrutinib with HD-MTX for newly diagnosed PCNSL patients. Additionally, the study explored the use of circulating tumor DNA (ctDNA) in cerebrospinal fluid (CSF) as a monitoring tool for treatment response.

Research objectives

The main objectives were to assess the treatment outcomes, adverse events, and genomic characteristics of PCNSL patients treated with HD-MTX and zanubrutinib combination therapy, and to investigate the potential of CSF ctDNA in disease surveillance.

Research methods

Nineteen eligible PCNSL patients were included in the study and received HD-MTX and zanubrutinib combination therapy. Clinical responses were evaluated, and ctDNA in CSF was analyzed using next-generation sequencing. Safety, treatment duration, and response were assessed.

Research results

The study demonstrated an overall response rate of 84.2% with the combination therapy, including complete and partial responses. Adverse events were mild and manageable. ctDNA levels in CSF were monitored and correlated with treatment response.

Research conclusions

Zanubrutinib combined with HD-MTX resulted in effective clinical responses in newly diagnosed PCNSL patients. The study highlighted the potential of CSF ctDNA for monitoring treatment response and disease surveillance. This combination therapy demonstrated promising safety and efficacy profiles.

Research perspectives

While the study results are promising, further research with larger patient cohorts and longer follow-up periods is needed to confirm the findings. The potential of zanubrutinib in different molecular subtypes of PCNSL and its long-term effects need to be explored. The clinical use of CSF ctDNA requires further investigation.

FOOTNOTES

Author contributions: The study conception and design were performed by Wang N, Chen FL, and Li WY; Data collection was performed by Wang N; All authors contributed to the data analysis and interpretation; Statistical analysis was performed by Wang N and Chen FL; The first draft of the manuscript was written by Wang N; All authors revised the manuscript.

Institutional review board statement: The study was reviewed and approved by the Guangdong Provincial People's Hospital Institutional Review Board.

Informed consent statement: All patients provided written informed consent to participate in this study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CASE REPORT

Rapid transformation of branched pancreatic duct-derived intraductal tubulopapillary neoplasm into an invasive carcinoma: A case report

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Abstract

BACKGROUND

Intraductal tubulopapillary neoplasm (ITPN) is a rare disease accounting for approximately 3% of all intraductal pancreatic tumors, with intraductal papillary mucinous neoplasm (IPMN) being one of the most common differential diagnoses. Both ITPN and IPMN display slow growth. A branched pancreatic duct type is commonly observed in IPMN, whereas ITPN derived from the branched pancreatic duct has been reported in a limited number of cases; hence, its pathogenesis remains unclear.

CASE SUMMARY

Here, we present the case of a patient with ITPN localized in a branched pancreatic duct, with poorly controlled irritable bowel syndrome. A contrast-enhanced computed tomography scan of the abdomen incidentally revealed a 5-mm oligemic nodule-like change in the body of the pancreas. Endoscopic ultrasound (EUS) indicated a 10-mm hypoechoic mass without any cystic structures that had grown within 2 mo. EUS-guided fine needle aspiration was performed for definitive diagnosis, and the findings suggested ductal papillary carcinoma. Distal pancreatectomy was performed, and the tumor was pathologically diagnosed as ITPN with an invasive cancerous component, pT3N1aM0, pStage IIB (International Cancer Control, 8th edition). The patient underwent

treatment with postoperative adjuvant chemotherapy (S-1 monotherapy); however, relapse was observed 1 year and 10 mo after surgical resection, and subsequent treatment involving a combination of chemotherapy and radiotherapy was administered. Maintenance therapy has since facilitated a stable disease state.

CONCLUSION
Regardless of the microscopic size of the neoplasm, early diagnosis of ITPN with EUS-guided fine needle aspiration and surgical resection are crucial.

Key Words: Intraductal tubulopapillary neoplasm; Pancreatic tumors; Neoplasia; Carcinoma; Pancreaticoduodenectomy; Case report

Core Tip: Intraductal tubulopapillary neoplasm (ITPN), a relatively rare intraductal pancreatic cancer, is frequently derived from the main pancreatic duct rather than from the branching ducts. Although tumors with larger diameters are more likely to develop into cancer, we reported a case of small ITPN originating from a bifurcated pancreatic duct rapidly developing into invasive cancer. The tumor was diagnosed and managed with endoscopic ultrasound-guided fine needle aspiration and surgery. However, relapse occurred 1 year and 10 mo postoperatively and was managed using chemotherapy and radiotherapy. Our case suggests the importance of early diagnosis and surgical resection even of a small ITPN.

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INTRODUCTION

Intraductal tubulopapillary neoplasm (ITPN) is a recently reported type of intraductal pancreatic tumor[1,2]. ITPN is extremely rare, accounting for approximately 3% of all intraductal tumors; its pathogenesis remains unclear[1]. Most ITPNs have a primary pancreatic ductal origin, while those growing exclusively in the branching duct are rare[3]. Despite ITPN being considered a precursor to invasive ductal adenocarcinoma, with 70% of cases associated with adenocarcinoma at diagnosis[4,5], ITPN progresses more slowly than conventional pancreatic ductal carcinoma. Further, even with invasive lesions, the prognosis is generally better than that for ductal carcinoma.

Herein, we present the case of a 59-year-old male with ITPN localized in a branched pancreatic duct.

CASE PRESENTATION

Chief complaints

A 59-year-old male was admitted to our hospital with a 3-4-year history of diarrhea and abdominal pain.

History of present illness

He had intermittent abdominal pain in the lower abdomen.

History of past illness

He was taking medication for irritable bowel syndrome, which was poorly controlled.

Personal and family history

He had no family history of malignancy.

Physical examination

The abdomen was soft and flat and showed no tenderness.

Laboratory examinations

Blood tests on admission showed an increased alkaline phosphatase level (363 IU/L, normal range: 38–113 IU/L); however, no other hepatobiliary enzyme levels were elevated. The tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal limits (Table 1).

Table 1 Laboratory findings

Test	Result
Hematology	
WBC	6300/μL
RBC	562 × 10^4/μL
Hb	16.7 g/dL
Ht	49.5%
Plt	23.4 × 10^4/μL
PT-INR	0.9
APTT	29.0 S
Biochemistry	
Blood sugar	92 mg/dL
CRP	0.0 mg/dL
TP	6.8 g/dL
Alb	4.4 g/dL
T-Bil	0.1 mg/dL
AST	19 IU/L
ALT	29 IU/L
γ-GTP	35 IU/L
ALP	363 IU/L
LDH	172 IU/L
AMY	60 IU/L
BUN	23 mg/dL
Cre	0.84 mg/dL
Na	139 mEq/L
K	4.5 mEq/L
Cl	105 mEq/L
Tumor maker	
CEA	3.4 ng/mL
CA19-9	< 2.0 ng/dL
DUPAN-2	36 U/mL
Span-1 antigen	< 3 U/mL

Alb: Albumin; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AMY: Amylase; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinogenic antigen; Cre: Creatinine; CRP: C-reactive protein; DUPAN-2: Duke pancreatic mono-clonal antigen type 2; Hb: Hemoglobin; Ht: Hematocrit; LDH: Lactate dehydrogenase; Plt: Platelet; PT-INR: Prothrombin time-international normalized ratio; RBC: Red blood cell count; T-Bil: Total bilirubin; TP: Total protein; WBC: White blood cell count; γ-GTP: Gamma-glutamyl transpeptidase.

Imaging examinations

Contrast-enhanced computed tomography of the abdomen incidentally revealed a 5-mm nodule-like mass in the pancreatic body. The nodule was not contrast-enhancing in the arterial phase and was faintly contrast-enhancing in the late phase (Figure 1A and B). Magnetic resonance imaging findings indicated a slightly high-intensity signal on diffusion-weighted images in the same area as that identified on computed tomography. However, identification of obvious neoplastic lesions or abnormal signal areas using T1- weighted and T2-weighted images and dynamic studies was difficult, and there was no change in the caliber of the main pancreatic duct (Figure 1C and D). Endoscopic ultrasound (EUS) performed 2 mo after the initial consultation revealed a 10-mm hypoechoic mass without a cystic structure in the body of the pancreas (Figure 2A). Using Sonazoid® (GE Healthcare, Chicago, IL, United States), a contrast agent, the

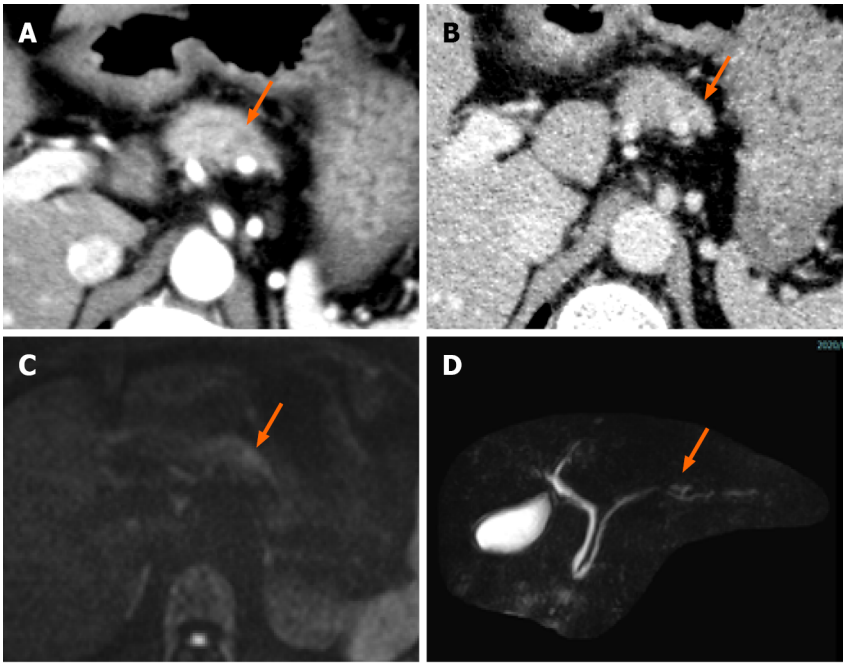

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Figure 1 Computed tomography and magnetic resonance imaging. A and B: A 5-mm nodule-like mass was observed in the pancreatic body; the nodule was not contrasted in the arterial phase, arrow (A) and was faintly contrasted in the late phase, arrow (B); C: Diffusion-weighted imaging showed a mild signal increase in the pancreatic body nodule noted on computed tomography, arrow; D: Magnetic resonance pancreatography showed no obvious dilatation or stenosis of the main pancreatic duct, arrow.

hypoechoic mass was identified as a hypovascular mass without contrast effect (Figure 2B).

Further diagnostic work-up

Because of the rapid increase in size within a short period and the possibility of malignancy, we performed EUS-guided fine needle aspiration (EUS-FNA) to obtain a definitive diagnosis. Histopathological examination revealed an atypical epithelium with papillary growth without a mucinous component. Some of the epithelium showed strong nuclear atypia, raising suspicion of an intraductal papillary carcinoma (Figure 2C and D). This was considered an indication for surgery, and a combined distal pancreatectomy and splenic resection were performed 5 mo after the initial detection of the tumor. Macroscopically, a 4 mm × 4 mm borderline brownish nodule and surrounding fibrosis measuring 12 mm × 8 mm × 12 mm were observed at a distance of 3.5 cm from the proximal lateral section of the pancreatic tail. No continuity with the main pancreatic duct was observed, and there was no dilation of the main pancreatic duct or notable changes in the surrounding pancreas (Figure 3). Microscopically, the tumor was located within the branched pancreatic duct and exhibited intraductal tubulopapillary growth with stromal invasion around the branched pancreatic duct (Figure 4A and B). There was no mucus production or cyst formation, and immunohistochemistry was positive for Mucin 1 (MUC1), negative for MUC2, partially positive for MUC5AC, and positive for MUC6 (Figure 4C-F). Mild perineural invasion but no lymphatic or venous invasion with two direct infiltrations in the peripancreatic lymph nodes were observed. Both dissection and pancreatic margins were negative.

FINAL DIAGNOSIS

The pathological diagnosis was ITPN (pT3N1aM0, pStageIIB, according to the eighth edition of the Union for International Cancer Control) with an invasive cancer component. The patient had no postoperative complications and was discharged from the hospital on postoperative day 13.

TREATMENT

The patient underwent treatment with postoperative adjuvant chemotherapy [S-1 monotherapy (80 mg/day)] for 6 mo following the treatment protocol for pancreatic cancer in Japan, and recurrence-free survival was maintained for 10 mo.

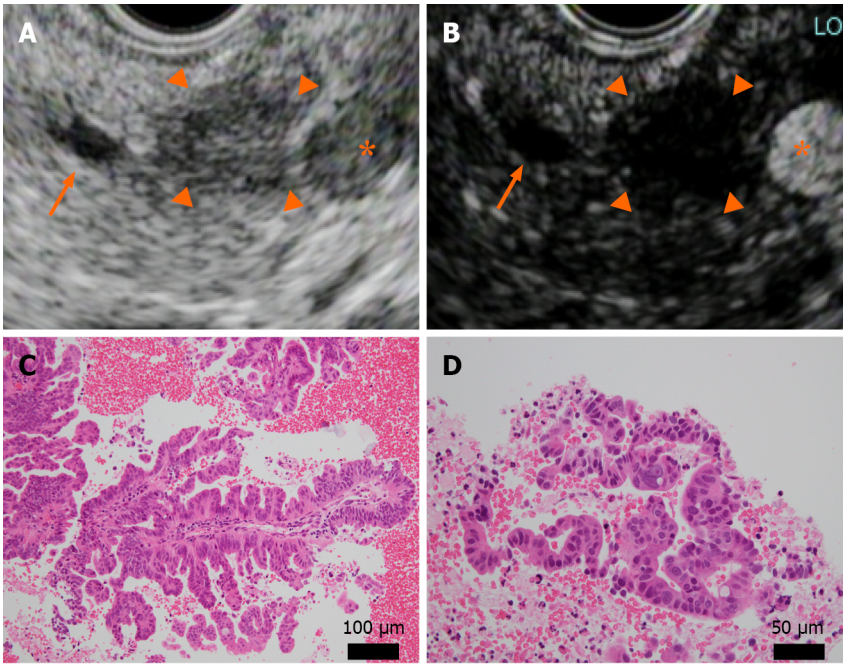

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Figure 2 Endoscopic ultrasound and histopathology (hematoxylin-eosin staining) at the time of endoscopic ultrasound-guided fine needle aspiration. A and B: A well-defined hypoechoic mass 10 mm in size was observed in the pancreatic body (A), arrowhead. The main pancreatic duct, arrow; splenic artery, asterisk. The mass was recognized as an oligo-hypoechoic mass with Sonazoid® contrast agent (B), arrowhead; C and D: Atypical epithelium with ductal papillary growth was seen. No intraductal papillary mucinous tumor-like mucus component was present. Original magnification was × 20 (C) and × 40 (D).

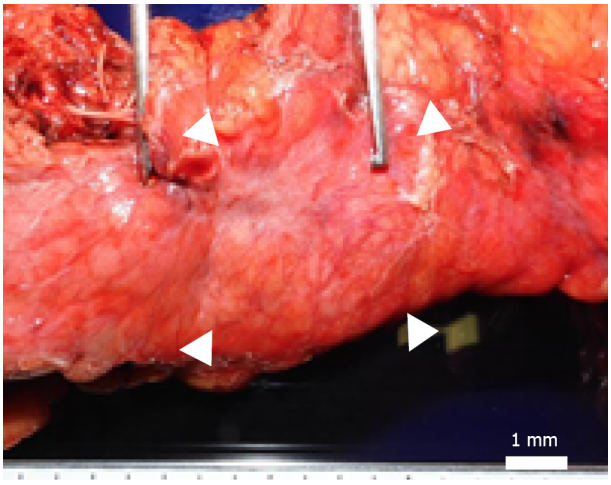

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Figure 3 Macroscopic findings. A well-defined brownish nodule measuring 4 mm × 4 mm bordering the pancreatic body; fibrosis extending to 8 mm × 12 mm in the periphery, arrowheads.

OUTCOME AND FOLLOW-UP

Magnetic resonance imaging performed at 1 year and 10 mo postoperatively revealed recurrence in the retroperitoneal lymph nodes at the surgical site (Figure 5). This postoperative recurrence was treated with oral S-1 in combination with radiation therapy (S-1: 120 mg for 4 wk, 100 mg for 2 wk, and 80 mg for 2 wk), and a reduction in the tumor size at the site of recurrence was observed. Following completion of radiotherapy (total 50 Gy), gemcitabine plus nab-paclitaxel (1000 mg/m^2, 125 mg/m^2) therapy was continued. To date, 2 years and 6 mo postoperatively, the patient's condition has remained in a stable state of disease[6].

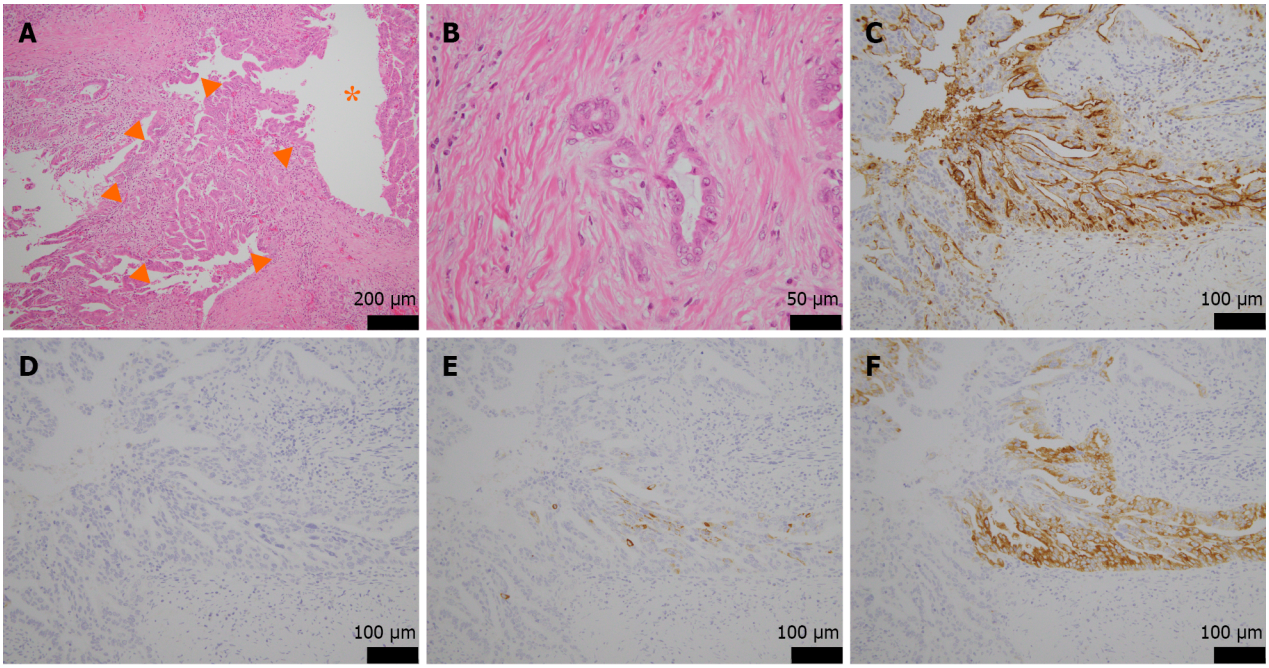

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Figure 4 Microscopic and immunohistological findings. A and B: Original magnification, (× 20, A), and (× 40, B). Tumors with papillary growth with adenoductal structures in the branching pancreatic ducts (asterisk) and some invasive, well-differentiated adenocarcinomas were present, arrowheads. There was no mucus production or cyst formation; C: Mucin 1 was positive; D: Mucin 2 was negative; E: Mucin 5AC was partially positive; F: Mucin 6 was positive. Original magnification was × 40.

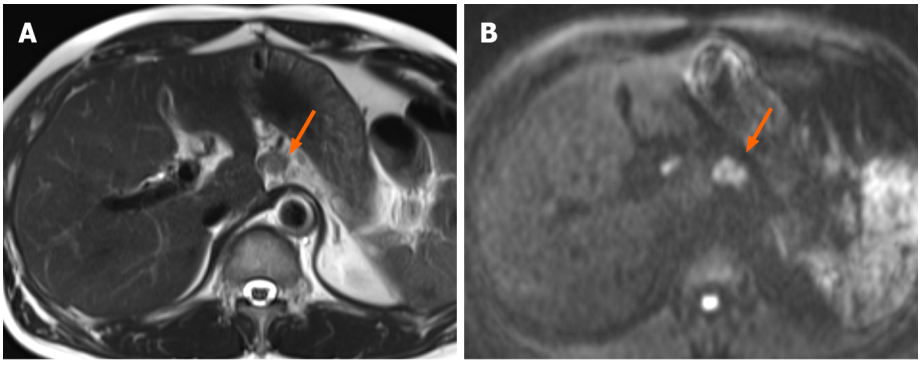

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Figure 5 Magnetic resonance imaging 1 year and 10 mo postoperatively. A: T2-weighted magnetic resonance imaging showed a small nodule in the postoperative area; B: Diffusion-weighted imaging showed a high signal in the same area, indicating recurrence in the retroperitoneal lymph nodes, arrow.

DISCUSSION

ITPN was described for the first time in 2009 by Yamaguchi *et al*[1] and is characterized by papillary growth in the pancreatic duct without mucous production, unlike intraductal papillary mucinous neoplasm (IPMN), which typically involves excessive mucin production. ITPN is a highly rare disease, with a frequency of 0.9% among pancreatic exocrine tumors and 3% among intraductal tumors[1]. The average patient age is 58 (25–82) years, and there are no sex differences [1,7]. The 5-year survival rate of ITPN is 81.5%, which is higher than that of pancreatic ductal carcinoma[3]. This type of tumor tends to grow slowly, and the average tumor diameter at the time of detection is 4.5 (0.5–15.0) cm[4].

ITPN is frequently compared to IPMN. Both are intraductal pancreatic tumors with a common intraductal growth pattern and the potential for malignant transformation; however, ITPN and IPMN differ in their immunohistological features. In the gross view, ITPN is a tumor that fills, expands, and proliferates in the pancreatic duct[1,2]. Although the caudal pancreatic duct may dilate due to its obstruction, the tumor does not have a cystic appearance or mucus deposits as in IPMN[1,2]. The Vaters papilla is not enlarged, and mucus outflow is not as observed in IPMN[1,2].

In IPMN, branched pancreatic duct types are common (88%), whereas in ITPN, this is a relatively rare feature (14%)[8]. Additionally, IPMN is positive for MUC5AC in all subtypes, including the oncocytic subtype. Conversely, ITPN is positive for MUC1 and MUC6 and negative for MUC2 and MUC5AC[9], which is consistent with our findings.

Surgical resection is the recommended treatment for ITPN[1,4,7,10]. Date *et al*[10] reported that among 37 patients with ITPN, the 1-year, 3-year, and 5-year overall survival (OS) rates after surgery were 97.3%, 80.7%, and 80.7%, respectively. Patients with ITPN-associated carcinoma had a favorable 5-year OS of 81.5% compared with the OS of those with ductal adenocarcinoma of the pancreas or IPMN-associated pancreatic cancer. Regarding ITPN prognosis, the recurrence-free survival rate tends to differ according to tumor size (< 4.0 cm *vs* > 4.0 cm) and Ki-67 labeling index (< 20% *vs* > 20%); however, these differences are not statistically significant[11]. Currently, there are no comprehensive reports on the efficacy of chemotherapy for ITPN. In the present case, when ITPN with invasive cancer was finally diagnosed, S-1 was administered as postoperative adjuvant chemotherapy following the standard treatment for conventional pancreatic ductal carcinoma in Japan[12]. It should be noted that the efficacy of S-1 for ITPN treatment is unknown.

Our report described a rare case of ITPN originating from a branched pancreatic duct that was incidentally observed in imaging studies and diagnosed using EUS-FNA. In this case, the tumor was small (3 cm in diameter), and the Ki-67 labeling index was approximately 50%, although it varied depending on the site. Despite being microscopic, the tumor rapidly increased in size, and the resected specimen demonstrated an invasive cancerous component. Thus, despite the general tendency of ITPN to grow slowly, in this case, the tumor rapidly progressed to invasive cancer and recurred 1 year and 10 mo postoperatively. As the occurrence of ITPN in the branched pancreatic duct is extremely rare, the nature of the tumor remains unclear.

CONCLUSION

Based on this case, we suggest that ITPN of the branched pancreatic duct type may have a worse prognosis than that of the main pancreatic duct. Further investigation of such cases is warranted. Moreover, early diagnosis of ITPN through EUS-FNA and subsequent surgical resection of the tumor are crucial. Further studies, especially multicenter studies, are required to validate our findings.

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FOOTNOTES

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