

A Systematic Review of Takotsubo Cardiomyopathy in Oncologic Cohorts

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ABSTRACT: Patients with cancer experience significant emotional, physical, and inflammatory stress, which can lead to Takotsubo cardiomyopathy (TCM), a reversible but acute type of ventricular failure. Understanding how TCM manifests in oncology is essential, as it frequently resembles acute coronary syndrome and overlaps with chemotherapy-related toxicity. In this systematic review of case reports, series, and registry data, we found that both malignancy itself and anti-neoplastic therapies are credible precipitants of TCM. Across more than 40 published cases, patients typically presented with chest pain, ST-segment changes, modest troponin elevation, and unobstructed coronaries. Imaging revealed transient apical ballooning and recovery of ejection fraction within weeks of drug withdrawal. Severe complications such as ventricular arrhythmias, thrombus formation, and embolic stroke were occasionally reported, and rechallenge with fluoropyrimidines carried a risk of recurrence. Overall, this review synthesized case-level evidence to clarify the presentation and mechanisms of TCM in oncology patients, with three main findings: (1) diagnostic features and clinical outcomes, (2) anti-neoplastic drugs most consistently associated with TCM, and (3) management strategies, including risks noted with rechallenge. These findings suggest that oncologists and cardiologists should maintain a low threshold for suspecting TCM in cancer patients presenting with ACS-like features, particularly during early cycles of fluoropyrimidines, HER2-targeted agents, and immune checkpoint inhibitors. Future research should prioritize prospective registries and mechanistic studies to guide evidence-based cardioprotective strategies in this vulnerable population.

KEYWORDS: Translational Medical Sciences, Disease Detection and Diagnosis, Cardio-oncology, Takotsubo Cardiomyopathy, Anti-neoplastic Agents.

■ Introduction

Cardio-oncology faces a persistent challenge in distinguishing chemotherapy-induced cardiotoxicity from other cardiac events in patients undergoing systemic anti-neoplastic therapies. Many of these patients already carry cardiovascular risk factors or preexisting disease, while simultaneously experiencing substantial physical and emotional stress during diagnosis and treatment.¹ Misattributing cardiac injury can have serious consequences: failing to recognize drug-related toxicity risks progressive, potentially irreversible damage, whereas wrongly discontinuing an effective anti-cancer agent for a non-drug cardiac event may compromise oncologic outcomes and survival.^{1,2} This clinical uncertainty highlights a pressing research gap in understanding stress-related cardiomyopathies within oncology.

Takotsubo cardiomyopathy (TCM) exemplifies this gap. It is a reversible, stress-related left-ventricular dysfunction that mimics *Acute Coronary Syndrome* (ACS) with chest pain, ECG changes, and modest troponin elevation but no obstructive coronary disease on angiography.^{1,2} The prototypical imaging pattern is transient apical ballooning with basal hyperkinesis.³ Although uncommon in the general population, registry and pooled analyses indicate that cancer is disproportionately represented among TCM cohorts, with prevalence estimates of 10–17% in modern series.⁴ Importantly, oncology-associated TCM appears more often linked to physical stressors and

carries worse short-term outcomes than emotionally triggered cases.^{2,4}

Case reports and small series further support this association, implicating several anti-neoplastic agents as temporal triggers of TCM. Fluoropyrimidines such as 5-fluorouracil and capecitabine are the most consistently reported, but targeted therapies, including trastuzumab and bevacizumab, have also been reported.^{1,5,6} These observations suggest that both cancer itself and its treatments act as precipitating factors.

Despite many reports, important uncertainties remain. Many reports lack complete diagnostic workups (for example, cardiac MRI or biopsy to exclude myocarditis), so attributing a single chemotherapeutic drug as the cause is therefore uncertain.^{2,6} Researchers caution that the psychological stresses of cancer care itself could induce TCM-like syndromes, so we must be careful before labeling an agent as definitively causative.² Taken together, the literature supports an association between cancer care and TCM, but also reveals inconsistent diagnostic completeness and variations in the reporting of timing, severity, and outcomes.^{1,2}

To address these gaps, this study compiles over 40 published case reports into a structured spreadsheet, creating an international case-level registry analysis. The review offers a unified viewpoint on Takotsubo cardiomyopathy in oncology by methodically extracting clinical presentation, diagnostic results, treatment approaches, and outcomes. The purpose of this synthesis is to shed light on diagnostic trends, identify the

drug classes most frequently involved, and guide useful management choices in cardio-oncology.

■ Methods

This study examined the prevalence and features of Takotsubo cardiomyopathy (TCM) in cancer patients, with an emphasis on cases associated with anti-neoplastic treatments. The objective was to compile disparate case-level material into an organized study that could shed light on management tactics, implicated agents, and diagnostic characteristics. This work was conducted as a literature review rather than an in-field clinical study. The dataset was built from published case reports, case series, registry analysis, and previous reviews. Keyword combinations like “Takotsubo Cardiomyopathy,” “TCM,” “TTS,” “Stress-Cardiomyopathy,” “apical ballooning,” “cancer,” “chemotherapy,” “antineoplastic,” and agent-specific terms like “5-fluorouracil,” “capecitabine,” “trastuzumab,” “bevacizumab,” and “immune checkpoint inhibitor” were used to collect data from PubMed/MEDLINE and ClinicalTrials.gov. Titles and abstracts were screened, full texts reviewed, and reference lists hand-searched to capture additional cases. Over 40 published case reports and series were extracted into a standardized spreadsheet documenting patient demographics, cancer type, drug exposure and timing, diagnostic findings, management, and outcomes, allowing comparison across cases and identification of recurring patterns. All information was derived from peer-reviewed sources, and no laboratory or clinical experimentation was performed; accordingly, no ethical approval or human or animal subject considerations were required.

Overview of Takotsubo Cardiomyopathy :

Takotsubo Cardiomyopathy (TCM), first characterized in Japan in the early 1990s, is a transient syndrome of left ventricular systolic dysfunction that commonly presents like an *Acute Coronary Syndrome* (ACS) with chest pain, ischemic electrocardiographic (ECG) changes, and modest troponin rise, yet without *Obstructive Coronary Disease* on angiography.^{1,3} The term “takotsubo” refers to the Japanese octopus trap-like shape formed by akinetic apical segments on ventriculography, while the basal segments remain hyperkinetic.³ Clinically, patients may present with chest pain, dyspnea, syncope, or hemodynamic compromise; complications can include heart failure, arrhythmia, left ventricular thrombus, embolic events, cardiogenic shock, and, very rarely, death.^{1,5}

Epidemiology and Clinical Patterns :

TCM is uncommon in the general population but is well documented across large registries and cohort studies. Modern registries show that over 90% of the typical patient is an older woman, predominantly in the postmenopausal age group, and many cases follow an identifiable emotional or physical stressor.^{5,7,8} As said before, TCM accounts for approximately 1–3% of patients presenting with a clinical picture suggestive of ACS.^{1,7} Emotional or physical stressors are identified in about two-thirds of cases, though up to one-third have no apparent precipitant.⁸ The InterTAK registry highlighted that

neurologic disease and psychiatric disorders are more prevalent in patients with TCM compared with other Acute Coronary Syndromes, suggesting a role for neurohumoral and stress-mediated pathways.⁸

Pathophysiology:

The pathophysiology of TCM is multifactorial, with sympathetic nervous system activation at its core. Early descriptions (1990s) by Dote and colleagues reported patients with multivessel coronary vasospasm producing reversible myocardial dysfunction, suggesting that epicardial spasm may explain a subset of cases.³ However, the pivotal study by Wittstein *et al.* demonstrated markedly elevated plasma catecholamine levels in patients with TCM, several-fold higher than in patients with ST-elevation MI, supporting a central catecholamine-mediated injury.⁹ At the myocardial level, excess catecholamines produce intracellular calcium overload, cAMP-mediated metabolic stress, and maladaptive β -adrenergic signaling, including a proposed β_2 -adrenergic switch to Gi coupling, changes that can provoke reversible myocyte stunning and regional wall-motion abnormalities characteristic of TCM.^{1,8,9} Coronary microvascular dysfunction has been shown by multimodality imaging and physiological studies, and likely causes transient tissue hypoperfusion even when epicardial arteries are angiographically normal.^{8,10} Early reports of simultaneous multivessel epicardial spasm indicate that coronary vasospasm explains a minority of cases in which spasm is demonstrable or provoked. The strong predominance of the postmenopausal age group of women and older patients points to sex- and age-related modifiers of susceptibility, such as loss of estrogenic cardioprotection and altered adrenergic or endothelial responsiveness.^{4,8} Genetic and molecular predispositions have been proposed but remain incompletely defined and definitely need further investigation.^{4,8} Figure 1 illustrates the prevailing model, in which an acute trigger induces a catecholamine surge that injures a susceptible myocardium through direct myocyte effects, microvascular dysfunction, and occasionally, epicardial spasm, producing the transient regional systolic failure seen in TCM.^{1,3,8,9,10}

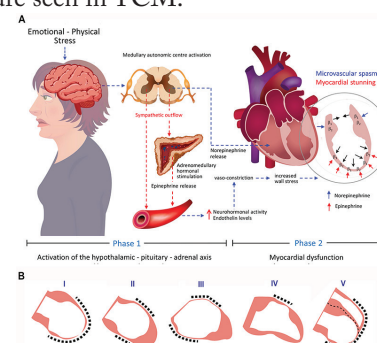


Figure 1: Diagram illustrating the pathophysiology of *Takotsubo Cardiomyopathy*. A catecholamine surge triggered by acute emotion or physical stimuli acts on β_1 - and β_2 -adrenergic receptors, producing direct myocardial injury, intracellular calcium overload, cAMP-mediated stress, and regional wall-motion abnormalities. These processes produce the characteristic left-ventricular contraction pattern, with apical akinesis or dyskinesis and basal hyperkinesis, which defines the typical presentation of TCM. Image reproduced from: Díaz-Navarro, R. Takotsubo Syndrome: The Broken-Heart Syndrome. *British Journal of Cardiology* 2021. <https://doi.org/10.5837/bjc.2021.011>.

Diagnostic Considerations:

Clinically, TCM must be distinguished from *Acute Myocardial Infarction*. Angiography remains essential to exclude obstructive coronary disease.⁸ Multimodality imaging, including ECG and cardiac magnetic resonance, refines the diagnosis by characterizing ventricular morphology, ruling out myocarditis, and detecting complications such as thrombus. The Mayo Clinic criteria remain widely used for case definition and research purposes.¹¹ Common diagnostic findings are summarized below in Figures 2 and 3.

Mayo Clinic Diagnostic Criteria for Takotsubo Cardiomyopathy:¹¹

- 1. Transient hypokinesis, akinesis, or dyskinesis of left ventricular mid-segments with/without apical involvement, regional wall motion abnormality extending beyond a single vascular territory, and a stressful trigger are often, but not always, present;
- 2. Absence of angiographic evidence of obstructive coronary disease or plaque rupture;
- 3. New ECG abnormalities consisting of ST elevation and/or T wave inversion with modest elevation in cardiac troponins;
- 4. Absence of pheochromocytoma and myocarditis

Electrocardiographic changes in TCM typically follow a dynamic pattern, evolving from initial ST-segment elevation to T-wave inversion and QT prolongation over days to weeks. Figure 2 illustrates these characteristic ECG alterations and their differential value relative to true myocardial infarction.

ST elevation	On presenting ECG <ul style="list-style-type: none">• 42-46% in precordial leads• Concomitant inferior or lateral leads• Uncommon if isolated in inferior or lateral leads	
ST depression	On presenting ECG <ul style="list-style-type: none">• Potential findings but less frequent (8%)	
Branch Block	On presenting ECG in 5% <ul style="list-style-type: none">• Left• Right	
T waves inversion	Evolution of ECG in 41% <ul style="list-style-type: none">• Diffuse and symmetric• Slow resolution and often partial resolution	
Pathologic Q waves	<ul style="list-style-type: none">• 6-31%• Transient Q waves are unusual	
QT segment	On presenting ECG <ul style="list-style-type: none">• Prolonged up to 500ms• Normalises in few days	
PR segment	On presenting ECG <ul style="list-style-type: none">• Prolonged	

Figure 2: Electrocardiographic (ECG) alterations are commonly observed in Takotsubo cardiomyopathy (TCM). These changes often mimic acute coronary syndromes, with ST-segment elevation in precordial leads being the most frequent finding. At the same time, ST depression, bundle branch block, and transient Q waves occur less often. T-wave inversion and QT prolongation are characteristic of the recovery phase, evolving over days to weeks, and may predispose patients to arrhythmias. To differentiate TCM from myocardial infarction and provide appropriate treatment, it is crucial to recognize this dynamic pattern of ECG anomalies. Image reproduced from: Pillitteri, M.; Brogi, E.; Piagnani, C.; Bozzetti, G.; Forfori, F. Perioperative Management of Takotsubo Cardiomyopathy: An Overview. *Journal of Anesthesia, Analgesia and Critical Care* 2024, 4 (1). <https://doi.org/10.1186/s44158-024-00178-y>.

Imaging is central to confirming the diagnosis of TCM, with coronary angiography used to exclude obstructive coronary disease and left ventriculography documenting the hallmark apical ballooning pattern. Figure 3 presents representative angiographic and ventriculographic findings from a typical TCM case, with arrows indicating the absence of obstructive lesions and panels demonstrating systolic apical ballooning with basal hyperkinesis.

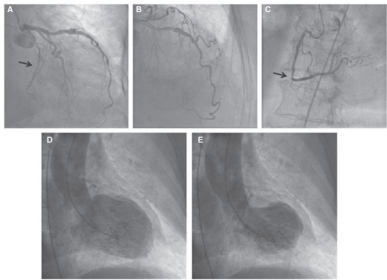


Figure 3: Typical TCM imaging. Coronary angiography in Panels A–C reveals no obstructive coronary artery disease (angiographic views are indicated by arrows). Panels D–E: left Ventriculography showing relative basal hyperkinesis and systolic apical ballooning. Image reproduced from: Citro, R.; Okura, H.; Ghadri, J. R.; Izumi, C.; Meimoun, P.; Izumo, M.; Dawson, D.; Kaji, S.; Eitel, I.; Kagiya, N.; Kobayashi, Y.; Templin, C.; Delgado, V.; Nakatani, S.; Popescu, B. A.; Bertrand, P.; Donal, E.; Dweck, M.; Galderisi, M.; Haugaa, K. H. Multimodality Imaging in Takotsubo Syndrome: A Joint Consensus Document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE). *European Heart Journal - Cardiovascular Imaging* 2020, 21 (11), 1184–1207. <https://doi.org/10.1093/ehjci/jeaa149>.

TTS And Cancer :

Cancer, a complex and long-term condition, can heighten the risk of Takotsubo Cardiomyopathy (TCM) due to the intense emotional and physical stress it causes. Emotional strain from diagnosis, chronic inflammation seen in many malignancies, and the physical toll of the disease or surgery are all recognized contributors to TCM.¹ Some studies also suggest that paraneoplastic mediators may interfere with cardiac adrenoceptors, potentially leading to contractile dysfunction.¹⁴ Cancer-related pain crises can also contribute to TCM development. The prevalence of malignancy in patients diagnosed with TTS is substantial, ranging from 4% to 29% across various studies, with some registries reporting rates as high as 15.8%. This indicates a notable overrepresentation of cancer patients within TCM cohorts when compared to the general population.¹⁴ These overlapping factors such as emotional distress, inflammation, treatment-related stressors, and paraneoplastic signaling are visually illustrated in Figure 4 (Figure 4).

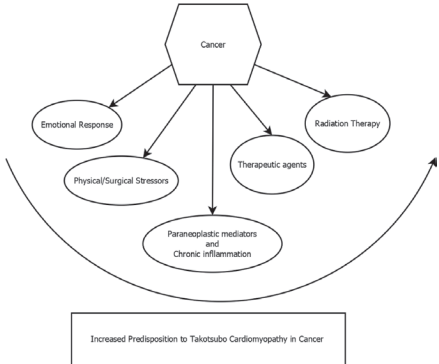


Figure 4: Through several interrelated processes, cancer may increase susceptibility to Takotsubo cardiomyopathy. While the disease itself and associated surgical treatments cause severe physical strain, the diagnosis and progression of cancer can cause substantial mental distress. Cardiovascular function can also be changed by the paraneoplastic mediators linked to cancer and the chronic inflammatory environment. Finally, various cancer treatments, including chemotherapy, targeted therapies, and radiation, may act as direct physiological triggers for the onset of TTS. Image reproduced from: Desai, A.; Noor, A.; Joshi, S.; Kim, A. S. Takotsubo Cardiomyopathy in Cancer Patients. *Cardio-Oncology* 2019, 5 (1). <https://doi.org/10.1186/s40959-019-0042-9>.

Anti-Cancer Therapy-Induced Cardiotoxicity:

The cardiotoxicity of various chemotherapeutic agents is a well-established concern in cardio-oncology.¹⁶ Cancer therapies can elicit a broad spectrum of adverse cardiac effects, including left ventricular dysfunction, myocardial ischemia, arrhythmias, hypertension, accelerated atherosclerosis, venous thromboembolism, myocarditis, and QT prolongation.¹⁷⁻²⁰ These complications restrict the use of certain chemotherapy drugs and represent a major cause of morbidity and mortality in cancer patients and survivors.^{18,21} A structured international registry-level analysis of over 40 published case reports is summarized in Table 1, detailing cancer types, implicated therapies, timing of TCM onset, and diagnostic features (Table 1).

Table 1: An Expanded International Case Registry analysis table: Takotsubo Cardiomyopathy Associated with Cancer Drugs, which compiles over 40 case reports and studies.

Reference	Age	Sex	Cancer Type	Chemotherapy/ Immunotherapy	TCM Onset	ECG Abnormality	Peak Troponin (ng/ml)
29	60	F	Stage III Colorectal	5-FU (FOLFOX)	1st cycle	STE II, III, aVF, V4-V6	0.38
30	62	F	Rectal Adenocarcinoma	5-FU + Levofolinate	6th cycle	STE V1-V3	0.82
53	57	F	Renal cell carcinoma	Sunitinib	N/A	STE	1.2
48	50	F	Breast (HER2+)	Trastuzumab	11th cycle	TWI V1-2, I, aVL	0.15
6	58	F	Colon	FOLFOX	1st cycle	Non-specific ST changes	0.64
31	81	F	Colorectal	5-FU → Capecitabine	1st Capecitabine	TWI anteroseptal, inferior, lateral	0.35
87	55	M	AML	Cytarabine + Daunorubicin	1st cycle	STE I, aVL, V5, V6	38.64
62	83	F	Melanoma	Ipilimumab	4th cycle	STE I, V2, V3	0.98
54	71	F	Renal cell carcinoma	Axitinib	1st cycle	Anterolateral STE	6.95
66	73	F	DLBCL	LACE (Lomustine, Cytarabine, Cyclophosphamide, Etoposide)	Final day	TWI anterolateral	N/A
67	45	F	Anal Canal	Intra-arterial/IV polychemotherapy	1st cycle	STE	N/A
35	55	M	Caecum	Capecitabine	1st cycle	STE V2-6, STD aVR, II, aVF	89
51	54	F	Breast (HER2+)	Pertuzumab + Trastuzumab	2nd cycle	STE, TWI	0.21
56	71	F	Thyroid	Lenvatinib	First cycle	STE, TWI	0.9
65	66	M	Melanoma	Checkpoint Inhibitor	2nd cycle	STE, TWI	1.1
60	N/A	Various	Various	Immune checkpoint inhibitors	Various	STE, TWI, Sinus Tachycardia, etc.	0.2-2.5
28	62	F	Rectal adenocarcinoma	5-FU	1st cycle	STE, TWI	0.8
46	55	M	Caecum	Capecitabine	1st cycle	STE V2-6, STD aVR, II, aVF	89
5	62	F	Colon	5-FU	1st cycle	STE, TWI	0.7
88	62	F	Bladder	Gemcitabine + Cisplatin	2nd cycle	STE, TWI	0.6
81	50	F	Breast (HER2+)	Trastuzumab	2nd cycle	STE, TWI	0.5
49	48	F	Breast (HER2+)	Trastuzumab	1st cycle	STE, TWI	0.4
41	66/61	M	Colon/NSCLC	Bevacizumab	1st & 2nd cycle	STE, Q waves	N/A

82	2 cases (N/A)	F	Breast/ Colorectal	Bevacizumab/ Riltuximab+Chemo	1st cycle	STE, TWI	N/A
50	63	F	Breast (HER2+)	Pertuzumab + Trastuzumab + Nab-paclitaxel	3rd cycle	STE, TWI	N/A
83	55	F	Breast (HR+/HER2-)	Palbociclib + Letrozole	N/A	STE V2-V4	6.8
73	72	F	Colon/NSCLC	Regorafenib	10 days	STE, TWI	N/A
57	60s	F	NSCLC	Afatinib	N/A	STE, TWI	N/A
55	60s	F	Thyroid	Lenvatinib	N/A	STE, TWI	N/A
84	59	M	Lymphoma	RCHOP/RCHVD	Pre-chemo	STE, TWI	N/A
85	57	F	NSCLC	Carboplatin, Pemetrexed, Pembrolizumab	1st cycle	STE, TWI	N/A
69	60s	F	Lung	Gemcitabine + Vinorelbine	1st cycle	STE, TWI	N/A
68	54	F	Colon (recurrent)	CRS + HIPEC	Post-op	STE, TWI	N/A
88	60s	F	Palliative (various)	None (pain crisis)	N/A	STE, TWI	N/A
89	54	F	Rectosigmoid	Surgery	Post-op	TWI, QT prolongation	N/A
90	65	F	Ovarian (metastatic)	None (diagnosis)	N/A	STE, TWI	N/A
14	38	F	Endocervical	Chemoradiation + Brachytherapy	During brachy	STE, TWI	N/A
86	2 cases (N/A)	F	Breast/ Endometrial	Tamoxifen/ Radiotherapy	Adjuvant	STE, TWI	N/A
36	55	F	Breast (metastatic)	Capecitabine	1st cycle	STE, TWI	N/A
37	60s	F	Colorectal	Capecitabine	1st cycle	STE, TWI	N/A
47	50s	F	Colorectal	5-FU → Capecitabine rechallenge	After the prior 5-FU TCM	STE, TWI	N/A
44	39	F	Breast (advanced)	Capecitabine	During therapy	STE, TWI	N/A
52	50s	F	Breast (HER2+)	Trastuzumab	Early cycle	STE, TWI, LV thrombus	N/A
58	60s	M	CLL (ibrutinib therapy)	Ibrutinib	N/A	Mid-cavitary variant, STE	N/A
59	2 cases (N/A)	F	NSCLC (EGFR+)	EGFR-TKI (erlotinib/gefitinib)	Early cycles	STE, TWI	N/A
63	62	M	HCC	Nivolumab (ICI)	3 weeks after start	STE, arrhythmias	N/A
64	50	F	Cancer (unspecified combo therapy)	ICI + chemo	N/A	STE, TWI	N/A
45	59	M	Sigmoid colon	FOLFOX	1st cycle	STE, hyperacute T waves	1

5-fluorouracil (5-FU):

5-Fluorouracil is a fluoropyrimidine analog that inhibits thymidylate synthase, disrupting DNA synthesis and inducing apoptosis in malignant cells.^{1,22} It is administered by bolus or continuous infusion for solid tumors, most prominently colorectal, gastric, esophageal, and pancreatic cancers, and serves as a backbone in combination regimens such as FOLFOX and FOLFIRI with leucovorin modulation.^{23,24} Cardiotoxicity is well described, with overall cardiovascular event rates reported between 1.5% and 18% in clinical series, and spans vasospastic angina, arrhythmias, myocardial infarction, heart failure, and stress cardiomyopathy.^{5,25-27} Various case studies of cancer therapy-induced TCM are summarized in Table 1 (Table 1).

Multiple case reports have supported the association between 5-FU and Takotsubo cardiomyopathy. Kobayashi *et al.*

described a 62-year-old woman receiving first-cycle 5-FU for rectal adenocarcinoma who developed chest pain with ST-segment elevation; angiography revealed no obstructive coronary disease, and imaging demonstrated apical ballooning, consistent with TCM.²⁸ Basselin *et al.* reported a 60-year-old woman on first-cycle FOLFOX who presented with diffuse ST elevation and modest troponin rise, with ventriculography confirming apical dyskinesis;²⁹ the Naranjo adverse drug reaction scale indicated a probable relationship between 5-FU and TCM with a score of 8.^{1,29} Grunwald *et al.* described TCM after the sixth cycle of 5-FU plus leucovorin in rectal adenocarcinoma, showing that susceptibility can persist beyond initial exposure.³⁰ Ozturk *et al.* detailed an FOLFOX-treated patient who presented with an ACS-like picture and was ultimately diagnosed with TCM, underscoring the need for angiography and multimodality imaging to exclude obstructive CAD and myocarditis.⁶

Across reported cases, onset is most often during or immediately after continuous infusion, frequently in the first cycle, and the clinical pattern includes chest pain, ST-segment elevation or T-wave inversion, modest troponin elevation, unobstructed coronaries, and transient reduction in left ventricular ejection fraction with recovery within weeks after cessation.^{5,31,32} Severe complications have been described, including ventricular fibrillation and shock, although most patients recover with supportive care and guideline-based TCM management.¹ Mechanistically, 5-FU may provoke epicardial vasospasm in a subset of patients, supported by experimental and clinical observations, while others demonstrate microvascular dysfunction and catecholamine surges aligned with canonical TCM pathways.^{6,9} Broader toxicology series and pharmacovigilance reviews reinforce the plausibility of direct and indirect cardiotoxic mechanisms with fluoropyrimidines.³²⁻³⁴

Rechallenge after 5-FU-associated TCM is controversial. Abdelrahman *et al.* reported successful capecitabine rechallenge following 5-FU-induced TCM; however, other reviews describe high rates of recurrent cardiotoxicity and deaths with re-exposure to fluoropyrimidines, arguing for caution and individualized, multidisciplinary decision-making.³⁴⁻³⁷ When oncologic necessity is compelling, consideration of alternative regimens, inpatient monitoring, and preventive strategies for vasospasm may be appropriate, with strict adherence to TCM imaging and supportive therapy standards.^{10,38}

Taken together, the evidence places 5-FU among the most consistent chemotherapeutic triggers of TCM. The syndrome typically arises during early infusion, presents with ACS-like features in the absence of obstructive coronary disease, and resolves with drug cessation and supportive care. Because recurrence with rechallenge is not rare, decisions to re-expose should weigh oncologic benefit against cardiotoxic risk in a multidisciplinary framework.^{1,5}

Bevacizumab:

Bevacizumab is a recombinant humanized monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A), thereby inhibiting angiogenesis and reducing tumor vascularization. By blocking VEGF signaling, bev-

acizumab enhances the efficacy of cytotoxic chemotherapy through decreased interstitial pressure and improved drug delivery to tumor tissue.^{18,39} Clinically, it is approved in combination regimens for metastatic colorectal cancer, non-small cell lung cancer, renal cell carcinoma, and several gynecologic malignancies.⁵⁴

The cardiovascular safety profile of bevacizumab has been a consistent concern in cardio-oncology. Hypertension is the most common adverse effect, but arterial thromboembolism, myocardial ischemia, heart failure, and arrhythmias have also been reported.^{21,40} Mechanistic studies suggest that VEGF inhibition disrupts endothelial nitric oxide signaling, reduces vascular repair capacity, and promotes microvascular dysfunction, all of which may predispose to myocardial injury and stress cardiomyopathy.³⁹ Inflammatory cytokine release and impaired coronary microcirculation have also been proposed as contributors to reversible left ventricular dysfunction in this setting.¹⁸

In sum, the evidence indicates that bevacizumab can act as a rare but plausible trigger for TCM in susceptible oncology patients. Proposed mechanisms include VEGF-related endothelial dysfunction, microvascular ischemia, and inflammatory signaling, all of which align with known pathways of stress cardiomyopathy. Although reported cases remain limited, clinicians should be alert to ACS-like presentations in patients receiving bevacizumab, especially those with existing cardiovascular risk factors. Prompt recognition, angiographic exclusion of obstructive disease, and supportive care are critical, as systolic function typically recovers once the drug is discontinued.³⁹⁻⁴¹

Capecitabine:

Capecitabine is an oral fluoropyrimidine prodrug that converts enzymatically to 5-fluorouracil (5-FU), with the final step catalyzed by thymidine phosphorylase, an enzyme concentrated in tumor tissue. This tumor-targeted activation was intended to improve tolerability compared to intravenous 5-FU while preserving antitumor activity.²³ Since its approval, capecitabine has been widely used in the treatment of colorectal, gastric, pancreatic, and breast cancers, either as monotherapy or in combination regimens such as CAPOX and XELOX.²⁵

However, clinical experience has demonstrated that capecitabine's cardiovascular toxicity profile is very similar to that of 5FU. Retrospective analyses report cardiotoxicity rates of approximately 3–9%, with manifestations ranging from angina and arrhythmias to myocardial infarction, cardiogenic shock, and sudden cardiac death.^{17,18,42} Symptoms typically develop within the first 72 hours of therapy and resolve after discontinuation, although severe complications have been described.

The most widely accepted mechanism is coronary vasospasm, supported by angiographic and clinical observations, but additional explanations include direct endothelial injury, prothrombotic effects, and immune-mediated myocardial inflammation.^{42,43} Experimental studies also suggest that fluoropyrimidines can impair microvascular function and mi-

tochondrial energetics, creating a substrate for stress-induced cardiomyopathy.³²

To date, seven cases of capecitabine-induced Takotsubo cardiomyopathy have been reported (Table 1). Molteni *et al.* described a 39-year-old woman with advanced breast cancer who developed acute chest pain and transient left ventricular dysfunction during capecitabine therapy, with full recovery after discontinuation of the drug.⁴⁴ Y-Hassan *et al.* reported a woman with advanced gastric cancer who presented with ST-segment elevation and classic wall-motion abnormalities, again resolving completely.⁴⁵ Endo *et al.* detailed a case complicated by both cardiomyopathy and multifocal cerebral leukoencephalopathy during capecitabine therapy.⁴⁶ Qasem *et al.* described a metastatic breast cancer patient who developed TCM during the first cycle of treatment, with unobstructed coronaries and normalization of function within weeks.³⁶ Abdelrahman *et al.* documented a rechallenge scenario in which capecitabine was successfully reintroduced after prior 5-FU-induced TCM under close monitoring.⁴⁷ Bhardwaj *et al.* reported a 47-year-old woman with metastatic breast cancer who developed chest pain, ST-elevation, and apical ballooning during her first cycle, with full recovery.³⁵ Abdelmaseih *et al.* presented a colorectal cancer patient with ACS-like features who was ultimately diagnosed with TCM and recovered after cessation.³⁷ Across these reports, patients ranged from middle-aged to elderly, had no prior coronary artery disease, typically developed symptoms during the first cycle, and all regained left ventricular function within 1–4 weeks.

Across these reports, consistent features emerge: patients were between 47 and 81 years of age, without prior coronary artery disease, and most developed symptoms during the first cycle of therapy. Presentations included chest pain, ECG changes with modest troponin elevation, and unobstructed coronaries on angiography. All patients demonstrated transient left ventricular systolic dysfunction with recovery of ejection fraction within 1–4 weeks after cessation of therapy.

Taken together, these findings indicate that capecitabine, like 5-FU, can act as a rare but credible trigger of Takotsubo cardiomyopathy. Clinicians should maintain vigilance for ACS-like presentations in patients receiving capecitabine, particularly during early cycles, and weigh the risks of rechallenge against oncologic necessity in a multidisciplinary framework.

Trastuzumab:

Trastuzumab is a recombinant humanized monoclonal antibody targeting the extracellular domain of the HER2 receptor, a member of the epidermal growth factor receptor family. By blocking HER2 signaling, trastuzumab inhibits tumor cell proliferation and survival, and it has become a cornerstone of therapy for HER2-positive breast and gastric cancers.¹⁷ Its introduction dramatically improved outcomes in these malignancies, but it also established a new paradigm of targeted therapy-related cardiotoxicity.

The most recognized cardiac complication of trastuzumab is left ventricular systolic dysfunction and heart failure, often reversible with drug discontinuation and standard therapy.³⁸ Unlike anthracyclines, trastuzumab does not cause cumulative

dose-dependent myocyte necrosis; instead, it interferes with HER2-mediated survival pathways in cardiomyocytes, impairing stress adaptation and repair.³⁹ This mechanism provides a biologic rationale for reversible dysfunction, but it also suggests susceptibility to stress-induced syndromes such as Takotsubo cardiomyopathy (TCM).

Several published cases have directly linked trastuzumab with TCM. Khanji *et al.* described a patient who developed acute chest pain and ST-segment elevation after trastuzumab infusion, with unobstructed coronaries and apical ballooning consistent with TCM.⁴⁸ Burgy *et al.* reported a woman who had postoperative TCM and was later re-treated with trastuzumab without recurrence, highlighting the complexity of re-exposure decisions.⁴⁹ Lees *et al.* presented a case of TCM during anti-HER2 therapy for metastatic breast cancer, again with full recovery of ventricular function. Matsumoto *et al.* reported a case of TCM triggered by an infusion reaction to trastuzumab, pointing to the impact of acute stress responses.⁵⁰ Patruno *et al.* described TCM during dual HER2 blockade with pertuzumab and trastuzumab, raising concern about increased risk.⁵¹ Patel *et al.* most recently described a complex case of trastuzumab-induced TCM with left ventricular thrombus and embolic stroke, showing that although recovery is common, major problems can happen.⁵²

The majority of patients across these reports were female and had HER2-positive breast cancer, which usually manifested during or soon after trastuzumab infusion. Chest discomfort, ST-segment elevation, mild troponin increase, unobstructed coronaries, and temporary apical ballooning were among the clinical characteristics. After trastuzumab was stopped, left ventricular function recovered in almost all cases within a few weeks, although there have been a few documented unusual side effects, including thrombus formation.

Overall, the data suggest that trastuzumab may be a rare cause of Takotsubo cardiomyopathy, even though it is mainly linked to reversible LV dysfunction. The suggested mechanism combines acute stress reactions during infusion with impairment of HER2-mediated cardioprotective signaling. Rechallenge decisions should be made on an individual basis within a multidisciplinary cardio-oncology framework, and clinicians should remain vigilant for ACS-like symptoms in patients receiving trastuzumab, especially early in therapy.

Tyrosine Kinase Inhibitors (TKIs):

Tyrosine kinase inhibitors (TKIs) are small-molecule agents that target intracellular signaling pathways essential for tumor growth and angiogenesis. By inhibiting receptors such as VEGFR, PDGFR, EGFR, and RET, TKIs have become central to the treatment of renal cell carcinoma, thyroid cancer, and non-small cell lung cancer. Their cardiovascular safety profile, however, has raised concern, with hypertension, QT prolongation, heart failure, and ischemic events well documented.^{39,40} More recently, several TKIs have been implicated in TTS, suggesting that endothelial dysfunction, microvascular ischemia, and acute hypertensive stress may converge with canonical catecholamine-mediated pathways to trigger this syndrome.

Sunitinib was the first TKI linked to TCM, with Numico *et al.* describing a renal cancer patient who developed acute chest pain and ST-segment elevation during therapy; angiography revealed unobstructed coronaries, and ventricular function normalized after drug withdrawal.⁵³ *Axitinib* has also been implicated, with Ovadia *et al.* reporting a patient who developed apical ballooning and transient systolic dysfunction consistent with TCM, again resolving after cessation.⁵⁴ *Lenvatinib* has been associated with multiple cases: Chae *et al.* described a thyroid cancer patient who developed both posterior reversible encephalopathy syndrome and TCM while on lenvatinib,⁵⁵ while Fashafsha *et al.* reported another thyroid cancer case in which lenvatinib triggered TCM, with recovery after discontinuation.⁵⁶ *Afatinib* has similarly been implicated, with Ramos *et al.* presenting a non-small cell lung cancer patient who developed TCM during therapy, characterized by apical ballooning and normalization of function within weeks.⁵⁷ Beyond VEGF and EGFR inhibitors, Giza *et al.* reported a mid-cavitary variant of TCM in a patient receiving the Bruton's tyrosine kinase inhibitor *ibrutinib*, expanding the spectrum of chemotherapy-associated TCM beyond the typical apical form.⁵⁸ Most recently, Tanaka *et al.* described two additional cases of TCM during EGFR-TKI therapy for non-small cell lung cancer with EGFR mutations, underscoring that this may represent a broader class effect.⁵⁹

Across these reports, patients typically presented with chest pain, ST-segment elevation, modest troponin rise, and unobstructed coronaries, with echocardiography or ventriculography confirming transient wall-motion abnormalities. Most cases occurred early in therapy, often within the first cycles, and all demonstrated recovery of left ventricular function within 1–4 weeks after cessation.

Taken together, these findings indicate that TKIs, though mechanistically distinct from fluoropyrimidines and monoclonal antibodies, can act as rare but credible triggers of Takotsubo cardiomyopathy. The proposed mechanisms include VEGF-mediated endothelial dysfunction, acute hypertensive stress, and microvascular ischemia, which align with canonical catecholamine-driven pathways. Clinicians should maintain vigilance for ACS-like presentations in patients receiving TKIs, particularly during early cycles, and weigh oncologic benefit against cardiotoxic risk in a multidisciplinary framework.

Immune Checkpoint Inhibitors (ICIs):

Immune Checkpoint Inhibitors (ICIs) Immune checkpoint inhibitors (ICIs) such as *ipilimumab*, *nivolumab*, *pembrolizumab*, and *atezolizumab* have revolutionized the treatment of melanoma, lung cancer, and other solid tumors by unleashing antitumor immunity through blockade of *CTLA-4* or *PD-1/PD-L1* pathways. While their most recognized cardiovascular toxicities include myocarditis, pericarditis, and arrhythmias, a growing body of evidence implicates ICIs in TCM. The proposed mechanisms include immune-mediated myocardial inflammation, cytokine surge, and catecholamine excess triggered by systemic immune activation, which converge with canonical stress-cardiomyopathy pathways.^{60,61}

The first published case was by Geisler *et al.*, who described a melanoma patient treated with ipilimumab who developed acute chest pain and apical ballooning consistent with TCM, with full recovery after discontinuation.⁶² Tan *et al.* reported a 62-year-old man with hepatocellular carcinoma who developed concomitant myopericarditis and TCM three weeks after nivolumab, presenting with ST-segment elevation and ventricular arrhythmias; coronary angiography was normal, and ventricular function normalized with supportive care.⁶³ Yamada *et al.* described a cancer patient receiving combination therapy, including an ICI, who developed ACS-like symptoms and was ultimately diagnosed with TCM, underscoring the diagnostic challenge in polytherapy settings.⁶⁴ Serzan *et al.* presented a series of ICI-associated TCM cases, including patients treated with nivolumab and pembrolizumab, all of whom demonstrated transient LV dysfunction with recovery after drug withdrawal.⁶⁵ More recently, systematic reviews by Kyriakoulis *et al.* and Trontzas *et al.* synthesized all published cases to date, confirming that TCM has been reported across multiple ICIs, including ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab.⁶⁰

Across these reports, patients typically presented with chest pain, ST-segment elevation or T-wave inversion, modest troponin rise, and unobstructed coronaries, with echocardiography or ventriculography confirming transient wall-motion abnormalities. Most cases occurred within the first few cycles of therapy, and all demonstrated recovery of left ventricular function within weeks after cessation. In sum, these findings indicate that ICIs, while primarily associated with myocarditis, can also act as rare triggers of Takotsubo cardiomyopathy. The overlap of immune-mediated inflammation and catecholamine-driven stress responses likely explains this association. Clinicians should maintain vigilance for ACS-like presentations in patients receiving ICIs, particularly early in therapy, and decisions regarding rechallenge should be individualized within a multidisciplinary cardio-oncology framework.

Polychemotherapy Regimens:

Takotsubo cardiomyopathy has also been described in the context of multi-agent chemotherapy, where attribution to a single drug is not possible. Malley *et al.* reported a patient who developed acute chest pain and transient apical ballooning after *combination chemotherapy*, with full recovery following supportive care.⁶⁶ Similarly, Coen *et al.* described TCM in a patient treated with a polychemotherapy regimen for anal canal carcinoma, and their accompanying review emphasized that heterogeneous regimens, not only fluoropyrimidines, can precipitate the syndrome.⁶⁷ These cases highlight the cumulative cardiotoxic stress that may arise from multi-drug exposure.

Other Oncologic Triggers:

Beyond systemic therapy, oncologic interventions themselves have been implicated in TCM. Vieira *et al.* reported a case of ventricular fibrillation arrest and subsequent TCM during *brachytherapy* for endocervical adenocarcinoma, with unobstructed coronaries on angiography.¹⁴ Moldovan *et al.* described life-threatening TCM following cytoreductive sur-

gery with *hyperthermic intraperitoneal chemotherapy (HIPEC)* for recurrent colon cancer, underscoring perioperative stress as a potent trigger.⁶⁸ These reports illustrate that procedural and surgical stressors in oncology can act as direct precipitants of stress cardiomyopathy.

Miscellaneous Single-Agent Reports:

Several isolated case reports expand the spectrum of agents associated with TCM. Özbay *et al.* described TCM occurring shortly after administration of “non-cardiotoxic” chemotherapy with *vinorelbine* and *gemcitabine*, reinforcing that stress cardiomyopathy can follow agents without classic cardiotoxic profiles.⁶⁹ Additional scattered reports have implicated *oxaliplatin* and *cyclophosphamide* in ACS-like presentations ultimately diagnosed as TCM, though these remain rare and anecdotal.^{27,42} Collectively, these cases suggest that while certain drug classes carry stronger mechanistic links, virtually any oncologic therapy may act as a trigger in susceptible patients.

Mechanistic Pathways of Takotsubo Cardiomyopathy in Oncology (Pathophysiology):

Catecholamine Surge and Sympathetic Overdrive:

Microvascular dysfunction is another central mechanism. Imaging and invasive studies have shown impaired coronary flow reserve and abnormal microvascular reactivity in TCM patients despite angiographically normal epicardial arteries.⁷⁰ Endothelial dysfunction and impaired nitric oxide signaling contribute to transient ischemia at the tissue level, which aligns with the reversible nature of the syndrome. This mechanism is particularly relevant in oncology, as VEGF inhibitors and fluoropyrimidines are known to impair microvascular function and may exacerbate susceptibility to stress cardiomyopathy.¹

Epicardial Coronary Spasm:

Although less common, epicardial coronary spasm has been documented in a subset of patients. Early Japanese reports described multivessel spasm during angiography in TCM, suggesting that vasospasm can mimic or precipitate the syndrome.^{3,7} This mechanism is especially relevant in fluoropyrimidine-associated cases, where vasospasm is a well-recognized cardiotoxic effect.

Inflammatory and Immune Pathways:

Inflammatory activation also appears to play a role. Cardiac magnetic resonance often demonstrates myocardial edema without necrosis, consistent with cytokine-mediated injury.⁸ Immune checkpoint inhibitors provide a clinical link, as several cases of TCM have occurred in parallel with myocarditis or systemic immune activation, suggesting overlapping inflammatory and catecholamine-driven pathways.⁶⁰ Singh *et al.* emphasized that neurohormonal stress and immune dysregulation likely act in concert, producing a vulnerable substrate for transient dysfunction.⁷¹

Sex and Age Predisposition in Takotsubo Cardiomyopathy:

Epidemiologic studies consistently demonstrate that Takotsubo cardiomyopathy occurs predominantly in women, with

over 90% of cases reported in postmenopausal patients.⁷ The InterTAK registry confirmed this striking demographic pattern, noting that the typical patient is a woman in her sixth or seventh decade of life, often presenting after an identifiable emotional or physical stressor.⁸ Several mechanisms have been proposed to explain this predisposition. Loss of estrogen after menopause is thought to reduce cardioprotective signaling, impair endothelial function, and increase susceptibility to catecholamine-mediated injury.⁷² Experimental and clinical data also suggest that postmenopausal women exhibit altered β -adrenergic receptor responsiveness and greater coronary microvascular dysfunction, both of which may amplify the myocardial effects of acute stress.^{9,71}

In the oncology setting, this demographic vulnerability is particularly relevant. Cancer therapies that provoke sympathetic activation, endothelial stress, or inflammatory signaling may act on an already susceptible substrate, explaining why many reported cases of chemotherapy-associated TCM involve middle-aged or older women. Recognizing this pattern is clinically important, as it should heighten suspicion for TCM in postmenopausal women presenting with ACS-like symptoms during cancer treatment.^{7,8}

Oncologic Context:

Cancer itself may heighten susceptibility to TCM through chronic stress, systemic inflammation, and paraneoplastic mediators. Desai *et al.* highlighted that malignancy is over-represented in TCM cohorts, with prevalence estimates of 10–17% in modern registries.¹ Paraneoplastic cytokines and altered adrenergic receptor signaling may further sensitize the myocardium to stress. When combined with cardiotoxic therapies, these factors create a “two-hit” model in which both the underlying cancer and its treatment converge on the same catecholamine-microvascular axis.^{70,71}

Standard/Conventional Treatments and Prognosis:

The management of Takotsubo cardiomyopathy remains largely supportive, guided by principles of acute heart failure care and tailored to the hemodynamic profile of each patient. Initial evaluation requires exclusion of acute coronary syndromes through urgent angiography and multimodality imaging, with echocardiography and cardiac magnetic resonance playing central roles in confirming the diagnosis and identifying complications such as thrombus or myocarditis.^{8,10} Once obstructive coronary disease is ruled out, therapy is directed toward stabilizing ventricular function. Patients with reduced ejection fraction are typically treated with beta-blockers, ACE inhibitors or ARBs, and diuretics as needed, with continuation until recovery of systolic function, which usually occurs within weeks.^{8,72,75}

Complications require specific management strategies. In cases of left ventricular outflow tract obstruction, inotropes should be avoided, as catecholamine stimulation can worsen obstruction; instead, cautious beta-blockade and volume expansion are recommended.^{72,73,75} When the left ventricular thrombus is present, or the ejection fraction is severely depressed, anticoagulation is indicated until resolution is doc-

umented.⁸ Arrhythmias and QT prolongation are managed with telemetry, electrolyte optimization, and avoidance of QT-prolonging drugs.⁸ In patients with cardiogenic shock, vasopressors may be required, but catecholamine agents should be minimized; mechanical circulatory support such as ECMO or percutaneous ventricular assist devices can be considered in refractory cases, while intra-aortic balloon pump use is controversial in the presence of outflow obstruction.^{8,72,75}

Prognosis is generally favorable, with most patients achieving full recovery of ventricular function within four to eight weeks, as confirmed in large registry studies.⁷ Nevertheless, recurrence is possible, and long-term follow-up with echocardiography is advised. Perioperative and anesthetic management also requires vigilance, as acute stressors can precipitate recurrence; careful hemodynamic monitoring and avoidance of excessive sympathetic stimulation are recommended in surgical settings.¹³ Taken together, conventional therapy for TCM emphasizes supportive care, complication-specific strategies, and close follow-up, with outcomes that are typically excellent when the condition is promptly recognized and managed.

Ongoing Clinical Studies on The Mechanism of Novel Therapeutic Interventions in TCM:

Several ongoing and completed clinical studies provide context for Takotsubo cardiomyopathy (TCM) in oncology. The PSYCHONIC study (NCT03437642) explores psychosomatic determinants of stress cardiomyopathy, profiling psychological stressors and autonomic markers relevant to cancer patients.⁷⁰ The TTAC registry (NCT01944826) systematically captures the timing of cancer diagnosis and treatment relative to TCM onset, lending epidemiologic weight to the observed overrepresentation of malignancy in TCM cohorts.⁷⁴ The MAESTRO trial (NCT05793008) prospectively distinguishes primary versus secondary TCM, a classification particularly applicable to oncology, where therapy-related triggers dominate.⁷⁶ Complementing these, the Psychosocial Support study (NCT05977049) evaluates behavioral interventions to reduce anxiety in TTS survivors, offering a framework for supportive care that could be adapted to cancer populations.⁷⁷ Finally, the EACVI-INFLAME study (NCT07077304) standardizes multimodality imaging across inflammatory cardiovascular diseases, including TCM, directly addressing diagnostic rigor and complication tracking.⁷⁸ Together, these trials underscore the multifactorial nature of cancer-associated TCM and highlight the need for integrated psychosocial, epidemiologic, and imaging approaches to improve recognition and management (Table 2).

Table 2: Summary of selected clinical trials investigating Takotsubo cardiomyopathy.

Clinical Trials.gov ID	Design	Population	Primary endpoint
NCT03437642	Observational	Oncologic and cardiac patients with suspected or confirmed TCM	Association of psychosocial/autonomic profiles with TCM onset and outcomes
NCT01944826	Registry (observational)	TCM patients with and without malignancy	Prevalence/temporal association of cancer and therapy with TCM; imaging and short-term outcomes
NCT05793008	Prospective characterization	Adults with primary or secondary TTS	Phenotypic classification with imaging/biomarkers; clinical outcomes
NCT05977049	Interventional (behavioral)	Adults with prior TTS	Anxiety reduction at 12 months with a structured support program
NCT07077304	Observational	Patients with inflammatory CVD, including TCM	Diagnostic standardization and validation across echo/CMR/CT/nuclear for TCM and related conditions

■ **Results and Discussion**

Takotsubo cardiomyopathy (TCM) has progressed from a rare syndrome first described in Japan to a recognized clinical entity with distinct epidemiology, pathophysiology, and outcomes. Large registries such as InterTAK established their demographic profile, predominantly postmenopausal women, and highlighted the role of acute stressors and neurohumoral activation in its pathogenesis.^{7,8} Mechanistic studies confirmed catecholamine excess, microvascular dysfunction, and, in select cases, epicardial spasm as central drivers of transient myocardial stunning.^{9,70,73} These insights provided the foundation for exploring how cancer and its therapies intersect with TCM, given the profound physical, emotional, and inflammatory stressors inherent to oncology care.^{1,4}

This review demonstrates that malignancy is not only overrepresented in TCM cohorts but also shapes the clinical phenotype. Cancer patients more often present with secondary TCM triggered by illness or therapy, and their short-term outcomes appear worse than those of emotionally triggered cases.^{1,16} Case reports consistently implicate fluoropyrimidines, particularly 5-fluorouracil and capecitabine, as reproducible pharmacologic triggers, with mechanistic plausibility supported by vasospasm, microvascular dysfunction, and catecholamine surges.^{6,29,30} Targeted therapies such as trastuzumab and bevacizumab, as well as tyrosine kinase inhibitors and immune checkpoint inhibitors, have also been linked to TCM, underscoring the convergence of endothelial injury, adrenergic stress, and immune activation on a vulnerable myocardium.^{41,48,60,65} These drug-specific observations align with the broader mechanistic framework of TCM and reinforce the need for vigilance in oncology practice.

A major clinical dilemma is whether to discontinue or re-challenge cancer therapy after a TCM episode. While case reports and pharmacovigilance data support drug-induced TCM, many lack complete diagnostic workups, raising the

possibility that some events reflect stress cardiomyopathy from the cancer itself or its psychosocial burden.^{1,6} Prematurely discontinuing an effective anti-cancer agent can compromise oncologic outcomes, particularly when the drug is central to curative regimens.² Conversely, rechallenge carries a real risk of recurrence, as documented with fluoropyrimidines and other agents.^{37,47} This underscores the need for individualized, multidisciplinary decision-making that balances oncologic benefit against cardiotoxic risk, ideally supported by prospective data rather than isolated case reports.

The clinical studies summarized in Table 2 extend these observations by moving beyond anecdotal reports toward structured investigation. The TTAC registry (NCT01944826) and PSYCHONIC study (NCT03437642) explicitly address the cancer-TCM intersection, capturing epidemiology and psychosocial determinants. MAESTRO (NCT05793008) advances phenotypic classification by distinguishing primary from secondary TCM, a distinction highly relevant to oncology patients. The psychosocial support trial (NCT05977049) operationalizes the brain-heart axis by testing whether structured interventions can mitigate recurrence and improve quality of life. Finally, EACVI-INFLAME (NCT07077304) emphasizes diagnostic rigor through standardized multimodality imaging, addressing the persistent challenge of differentiating TCM from ACS or myocarditis. Together, these studies illustrate how the field is transitioning from descriptive case reports to prospective, mechanistic, and interventional research.

Despite these advances, important limitations remain. Much of the evidence linking chemotherapy and targeted therapies to TCM derives from case reports and small series, many of which lack complete diagnostic workups such as cardiac MRI or biopsy.^{1,6} Registries provide valuable epidemiologic insights but are often limited by referral bias and incomplete oncologic data. Clinical trials remain few, and several have unknown or inactive status, underscoring the need for sustained prospective enrollment.

Looking forward, future research should prioritize three directions. First, prospective registries that integrate oncology and cardiology data are needed to clarify the true incidence, timing, and outcomes of cancer-associated TCM. Second, mechanistic studies should explore how specific therapies—fluoropyrimidines, HER2-targeted agents, VEGF inhibitors, and immune checkpoint inhibitors—interact with adrenergic, endothelial, and immune pathways to precipitate TCM. Third, interventional trials are required to test preventive and therapeutic strategies, including pharmacologic prophylaxis, structured psychosocial support, and cardio-oncology monitoring frameworks. By combining mechanistic insight with prospective clinical data, the field can move toward evidence-based strategies that balance oncologic efficacy with cardiovascular safety.

■ Conclusion

Takotsubo cardiomyopathy represents a unique intersection of oncology and cardiology, where the physiological and psychological stresses of cancer, combined with the car-

diotoxic potential of modern therapies, create a heightened vulnerability to this reversible yet serious syndrome. Although most patients recover ventricular function, the occurrence of TCM in the setting of malignancy is associated with worse short-term outcomes and, critically, the potential interruption of life-saving cancer therapy. This review underscores that distinguishing true drug-induced TCM from other reversible cardiotoxicities remains a central challenge, as premature discontinuation of effective regimens can compromise oncologic survival, while rechallenge carries a risk of recurrence. Moving forward, careful case-by-case evaluation, integration of multimodality imaging, and prospective research into mechanisms and preventive strategies are essential to ensure that patients receive both optimal cancer treatment and vigilant cardiovascular protection.

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■ References

- Desai, A.; Noor, A.; Joshi, S.; Kim, A. S. Takotsubo Cardiomyopathy in Cancer Patients. *Cardio-Oncology* **2019**, *5* (1). <https://doi.org/10.1186/s40959-019-0042-9>.
- Madias, J. E. Is Takotsubo Syndrome in Patients Receiving Chemotherapy Drug-Specific? *World Journal of Clinical Cases* **2015**, *3* (2), 204. <https://doi.org/10.12998/wjcc.v3.i2.204>.
- Dote, K.; Sato, H.; Tateishi, H.; Uchida, T.; Ishihara, M. [Myocardial Stunning due to Simultaneous Multivessel Coronary Spasms: A Review of 5 Cases]. *Journal of Cardiology* **1991**, *21* (2), 203–214.
- Tini, G.; Arcari, L.; Raffaella Mistrulli; Follesa, F.; Cianca, A.; Sclafani, M.; Tocci, G.; Paolo Spallarossa; Battistoni, A.; Cacciotti, L.; Musumeci, B.; Barbato, E. A Contemporary Update on Cancer and Takotsubo Syndrome. *Frontiers in cardiovascular medicine* **2024**, *10*. <https://doi.org/10.3389/fcvm.2023.1301383>.
- Stephanie Hui-Su Lim; Sharon Mary Wilson; Hunter, A.; Hill, J.; Beale, P. Takotsubo Cardiomyopathy and 5-Fluorouracil: Getting to the Heart of the Matter. *Case Reports in Oncological Medicine* **2013**, *2013*, 1–4. <https://doi.org/10.1155/2013/206765>.
- Ozturk, M. A.; Ozveren, O.; Cinar, V.; Erdik, B.; Oyan, B. Takotsubo Syndrome. *Blood Coagulation & Fibrinolysis* **2013**, *24* (1), 90–94. <https://doi.org/10.1097/mbc.0b013e3283597605>.
- Templin, C.; Ghadri, J. R.; Diekmann, J.; Napp, L. C.; Bataiosu, D. R.; Jaguszewski, M.; Cammann, V. L.; Sarcon, A.; Geyer, V.; Neumann, C. A.; Seifert, B.; Hellermann, J.; Schwyzer, M.; Eisenhardt, K.; Jenewein, J.; Franke, J.; Katus, H. A.; Burgdorf, C.; Schunkert, H.; Moeller, C. Clinical Features and Outcomes of Takotsubo

- (Stress) Cardiomyopathy. *New England Journal of Medicine* **2015**, 373 (10), 929–938. <https://doi.org/10.1056/nejmoa1406761>.
8. Ghadri, J.-R.; Wittstein, I. S.; Prasad, A.; Sharkey, S.; Dote, K.; Akashi, Y. J.; Cammann, V. L.; Crea, F.; Galiuto, L.; Desmet, W.; Yoshida, T.; Manfredini, R.; Eitel, I.; Kosuge, M.; Nef, H. M.; Deshmukh, A.; Lerman, A.; Bossone, E.; Citro, R.; Ueyama, T. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. *European Heart Journal* **2018**, 39 (22), 2032–2046. <https://doi.org/10.1093/eurheartj/ehy076>.
 9. Wittstein, I. S.; Thiemann, D. R.; Lima, J. A. C.; Baughman, K. L.; Schulman, S. P.; Gerstenblith, G.; Wu, K. C.; Rade, J. J.; Bivalacqua, T. J.; Champion, H. C. Neurohumoral Features of Myocardial Stunning due to Sudden Emotional Stress. *New England Journal of Medicine* **2005**, 352 (6), 539–548. <https://doi.org/10.1056/nejmoa043046>.
 10. Citro, R.; Okura, H.; Ghadri, J. R.; Izumi, C.; Meimoun, P.; Izumo, M.; Dawson, D.; Kaji, S.; Eitel, I.; Kagiya, N.; Kobayashi, Y.; Templin, C.; Delgado, V.; Nakatani, S.; Popescu, B. A.; Bertrand, P.; Donal, E.; Dweck, M.; Galderisi, M.; Haugaa, K. H. Multimodality Imaging in Takotsubo Syndrome: A Joint Consensus Document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE). *European Heart Journal - Cardiovascular Imaging* **2020**, 21 (11), 1184–1207. <https://doi.org/10.1093/ehjci/jeaa149>.
 11. Madhavan, M.; Prasad, A. Proposed Mayo Clinic Criteria for the Diagnosis of Tako-Tsubo Cardiomyopathy and Long-Term Prognosis. *Herz* **2010**, 35 (4), 240–244. <https://doi.org/10.1007/s00059-010-3339-x>.
 12. Díaz-Navarro, R. Takotsubo Syndrome: The Broken-Heart Syndrome. *British Journal of Cardiology* **2021**. <https://doi.org/10.5837/bjc.2021.011>.
 13. Pillitteri, M.; Brogi, E.; Piagnani, C.; Bozzetti, G.; Forfori, F. Perioperative Management of Takotsubo Cardiomyopathy: An Overview. *Journal of Anesthesia, Analgesia and Critical Care* **2024**, 4 (1). <https://doi.org/10.1186/s44158-024-00178-y>.
 14. Vieira, A. C.; Ribeiro, M. F. S. A.; Lima, J.; Filho, J. S.; de Andrade Carvalho, H.; Mano, M. S. Takotsubo Syndrome Induced by Brachytherapy in a Patient with Endocervical Adenocarcinoma. *Cardio-oncology (London, England)* **2020**, 6 (1), 30. <https://doi.org/10.1186/s40959-020-00082-8>.
 15. Cameli, M.; Landra, F. Editorial: Case Reports in Heart Failure and Transplantation: 2022. *Frontiers in Cardiovascular Medicine* **2023**, 10. <https://doi.org/10.3389/fcvm.2023.1282064>.
 16. Cammann, V. L.; Annahita Sarcon; Ding, K. J.; Seifert, B.; Kato, K.; Davide Di Vece; Szawan, K. A.; Gili, S.; Jurisic, S.; Bacchi, B.; Micek, J.; Frangieh, A. H.; L. Christian Napp; Miłosz Jaguszewski; Bossone, E.; Citro, R.; Fabrizio D'Ascenzo; Franke, J.; Noutsias, M.; Knorr, M. Clinical Features and Outcomes of Patients with Malignancy and Takotsubo Syndrome: Observations from the International Takotsubo Registry. *Journal of the American Heart Association* **2019**, 8 (15). <https://doi.org/10.1161/jaha.118.010881>.
 17. Trapani, D.; Zagami, P.; Nicolò, E.; Pravettoni, G.; Curigliano, G. Management of Cardiac Toxicity Induced by Chemotherapy. *Journal of Clinical Medicine* **2020**, 9 (9), 2885. <https://doi.org/10.3390/jcm9092885>.
 18. Barachini, S.; Ghelardoni, S.; Varga, Z. V.; Mehanna, R. A.; Montt-Guevara, M. M.; Ferdinandy, P.; Madonna, R. Antineoplastic Drugs Inducing Cardiac and Vascular Toxicity – an Update. *Vascular Pharmacology* **2023**, 153, 107223. <https://doi.org/10.1016/j.vph.2023.107223>.
 19. Han, X.; Zhou, Y.; Liu, W. Precision Cardio-Oncology: Understanding the Cardiotoxicity of Cancer Therapy. *npj Precision Oncology* **2017**, 1 (1). <https://doi.org/10.1038/s41698-017-0034-x>.
 20. Peng, J.; Rushton, M.; Johnson, C.; Brezden-Masley, C.; Sulpher, J.; Chiu, M. G.; Graham, I. D.; Dent, S. An International Survey of Healthcare Providers' Knowledge of Cardiac Complications of Cancer Treatments. *Cardio-Oncology* **2019**, 5 (1). <https://doi.org/10.1186/s40959-019-0049-2>.
 21. de Wall, C.; Bauersachs, J.; Berliner, D. Cardiooncology—Dealing with Modern Drug Treatment, Long-Term Complications, and Cancer Survivorship. *Clinical & Experimental Metastasis* **2021**, 38 (4), 361–371. <https://doi.org/10.1007/s10585-021-10106-x>.
 22. Cobarro, L.; Valbuena-López, S.; Contreras, C.; Ugue-to, C.; Ruiz-Gutiérrez, I.; Peña-López, J.; Ruiz-Giménez, L.; López-Fernández, T. Immune Checkpoint Inhibitor-Related Stress Cardiomyopathy. *JACC: Case Reports* **2023**, 16, 101881. <https://doi.org/10.1016/j.jaccas.2023.101881>.
 23. Parker, W. B.; Cheng, Y. C. Metabolism and Mechanism of Action of 5-Fluorouracil. *Pharmacology & Therapeutics* **1990**, 48 (3), 381–395. [https://doi.org/10.1016/0163-7258\(90\)90056-8](https://doi.org/10.1016/0163-7258(90)90056-8).
 24. Goldberg, R. M.; Tabah-Fisch, I.; Bleiberg, H.; de Gramont, A.; Tournigand, C.; Andre, T.; Rothenberg, M. L.; Green, E.; Sargent, D. J. Pooled Analysis of Safety and Efficacy of Oxaliplatin plus Fluorouracil/Leucovorin Administered Bimonthly in Elderly Patients with Colorectal Cancer. *Journal of Clinical Oncology* **2006**, 24 (25), 4085–4091. <https://doi.org/10.1200/jco.2006.06.9039>.
 25. Heinemann, V.; von Weikersthal, L. F.; Decker, T.; Kiani, A.; Vehlting-Kaiser, U.; Al-Batran, S.-E.; Heintges, T.; Lerchenmüller, C.; Kahl, C.; Seipelt, G.; Kullmann, F.; Stauch, M.; Scheithauer, W.; Hielscher, J.; Scholz, M.; Müller, S.; Link, H.; Niederle, N.; Rost, A.; Höffkes, H.-G. FOLFIRI plus Cetuximab versus FOLFIRI plus Bevacizumab as First-Line Treatment for Patients with Metastatic Colorectal Cancer (FIRE-3): A Randomised, Open-Label, Phase 3 Trial. *The Lancet Oncology* **2014**, 15 (10), 1065–1075. [https://doi.org/10.1016/s1470-2045\(14\)70330-4](https://doi.org/10.1016/s1470-2045(14)70330-4).
 26. Labianca, R.; Beretta, G.; Clerici, M.; Frascini, P.; Luporini, G. Cardiac Toxicity of 5-Fluorouracil: A Study on 1083 Patients. *Tumori Journal* **1982**, 68 (6), 505–510. <https://doi.org/10.1177/030089168206800609>.
 27. Dalzell, J. R.; Samuel, L. M. The Spectrum of 5-Fluorouracil Cardiotoxicity. *Anti-Cancer Drugs* **2008**, 20 (1), 79–80. <https://doi.org/10.1097/cad.0b013e3283165f27>.
 28. Kobayashi, N.; Hata, N.; Yokoyama, S.; Takuro Shinada; Akihiro Shirakabe; Mizuno, K. A Case of Takotsubo Cardiomyopathy during 5-Fluorouracil Treatment for Rectal Adenocarcinoma. *Journal of Nippon Medical School* **2009**, 76 (1), 27–33. <https://doi.org/10.1272/jnms.76.27>.
 29. P D Cécile Basselin; T. Fontanges; Descotes, J.; Chevalier, P.; Bui-Xuan, B.; P D Gwennaelle Feinard; Quadiri Timour. 5-Fluorouracil-Induced Tako-Tsubo-like Syndrome. **2011**, 31 (2), 226–226. <https://doi.org/10.1592/phco.31.2.226>.
 30. Grunwald, M. R.; Howie, L.; Diaz, L. A. Takotsubo Cardiomyopathy and Fluorouracil: Case Report and Review of the Literature. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology* **2012**, 30 (2), e11–4. <https://doi.org/10.1200/JCO.2011.38.5278>.
 31. Knott, K.; Starling, N.; Rasheed, S.; Foran, J.; Cafferkey, C.; Rosen, S.; Nicholson, A.; Baksi, J.; Lyon, A. A Case of Takotsubo Syndrome Following 5-Fluorouracil Chemotherapy. *International Journal of Cardiology* **2014**, 177 (2), e65–e67. <https://doi.org/10.1016/j.ijcard.2014.09.154>.
 32. Tsibiribi, P.; Bui-Xuan, C.; Bui-Xuan, B.; Lombard-Bohas, C.; Duperret, S.; Belkhiria, M.; Tabib, A.; Maujean, G.; Descotes,

- J.; Timour, Q. Cardiac Lesions Induced by 5-Fluorouracil in the Rabbit. *Human & Experimental Toxicology* **2006**, *25* (6), 305–309. <https://doi.org/10.1191/0960327106ht628oa>.
33. Becker, K.; Erckenbrecht, J. F.; Aussinger, D.; Frieling, T. Cardiotoxicity of the Antiproliferative Compound Fluorouracil. *Drugs* **1999**, *57* (4), 475–484. <https://doi.org/10.2165/00003495-199957040-00003>.
34. Gianni, M.; Dentali, F.; Grandi, A. M.; Sumner, G.; Hiralal, R.; Lonn, E. Apical Ballooning Syndrome or Takotsubo Cardiomyopathy: A Systematic Review. *European Heart Journal* **2006**, *27* (13), 1523–1529. <https://doi.org/10.1093/eurheartj/ehl032>.
35. Bhardwaj, P. V.; Chaubey, V. K.; Islam, A. M. Capecitabine-Induced Takotsubo Cardiomyopathy: A Case Report. *The Permanente Journal* **2019**, *23*. <https://doi.org/10.7812/tpp/18.245>.
36. Qasem, A.; Bin Abdulhak, A. A.; Aly, A.; Moormeier, J. Capecitabine-Induced Takotsubo Cardiomyopathy: A Case Report and Literature Review. *American Journal of Therapeutics* **2016**, *23* (5), e1188–e1192. <https://doi.org/10.1097/mjt.0000000000000134>.
37. Abdelmaseih, R.; Blanco, A.; Abdelmasih, R.; Desai, K.; Pothan, J.; Patel, J.; Balaraman, R. Cardio-Oncology: Capecitabine Can Sometimes Be Heartbreaking Capecitabine-Induced Takotsubo Cardiomyopathy Case Report and Literature Review. *Current problems in cardiology* **2021**, *46* (8), 100854. <https://doi.org/10.1016/j.cpcardiol.2021.100854>.
38. Plana, J. C.; Galderisi, M.; Barac, A.; Ewer, M. S.; Ky, B.; Scherrer-Crosbie, M.; Ganame, J.; Sebag, I. A.; Agler, D. A.; Badano, L. P.; Banchs, J.; Cardinale, D.; Carver, J.; Cerqueira, M.; DeCara, J. M.; Edvardsen, T.; Flamm, S. D.; Force, T.; Griffin, B. P.; Jerusalem, G. Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography* **2014**, *27* (9), 911–939. <https://doi.org/10.1016/j.echo.2014.07.012>.
39. Touyz, R. M.; Herrmann, J. Cardiotoxicity with Vascular Endothelial Growth Factor Inhibitor Therapy. *npj Precision Oncology* **2018**, *2* (1). <https://doi.org/10.1038/s41698-018-0056-z>.
40. Mihalcea, D.; Memis, H.; Mihaila, S.; Vinereanu, D. Cardiovascular Toxicity Induced by Vascular Endothelial Growth Factor Inhibitors. *Life* **2023**, *13* (2), 366. <https://doi.org/10.3390/life13020366>.
41. Franco, T. Takotsubo Cardiomyopathy in Two Men Receiving Bevacizumab for Metastatic Cancer. *Therapeutics and Clinical Risk Management* **2008**, *Volume 4*, 1367–1370. <https://doi.org/10.2147/tcrm.s3960>.
42. Stewart, T.; Pavlakakis, N.; Ward, M. Cardiotoxicity with 5-Fluorouracil and Capecitabine: More than Just Vasospastic Angina. *Internal Medicine Journal* **2010**, *40* (4), 303–307. <https://doi.org/10.1111/j.1445-5994.2009.02144.x>.
43. Saif, M. W.; Shah, M. M.; Shah, A. R. Fluoropyrimidine-Associated Cardiotoxicity: Revisited. *Expert Opinion on Drug Safety* **2009**, *8* (2), 191–202. <https://doi.org/10.1517/14740330902733961>.
44. Molteni, L. P.; Rampinelli, I.; Cergnul, M.; Scaglietti, U.; Paino, A. M.; Noonan, D. M.; Bucci, E. O.; Gottardi, O.; Albini, A. Capecitabine in Breast Cancer: The Issue of Cardiotoxicity during Fluoropyrimidine Treatment. *The Breast Journal* **2010**, *16*, S45–S48. <https://doi.org/10.1111/j.1524-4741.2010.01004.x>.
45. Y-Hassan, S.; Tornvall, P.; Törnerud, M.; Henareh, L. Capecitabine Caused Cardiogenic Shock through Induction of Global Takotsubo Syndrome. *Cardiovascular revascularization medicine: including molecular interventions* **2013**, *14* (1), 57–61. <https://doi.org/10.1016/j.carrev.2012.10.001>.
46. Endo, A.; Yoshida, Y.; Nakashima, R.; Takahashi, N.; Tanabe, K. Capecitabine Induces Both Cardiomyopathy and Multifocal Cerebral Leukoencephalopathy. *International Heart Journal* **2013**, *54* (6), 417–420. <https://doi.org/10.1536/ihj.54.417>.
47. Abdelrahman, M.; McCarthy, M. T.; Haliana Yusuf, Osman, N. Successful Capecitabine Rechallenge Following 5-Fluorouracil-Induced Takotsubo Syndrome. *Oxford Medical Case Reports* **2016**, *2016* (3), 47–50. <https://doi.org/10.1093/omcr/omv072>.
48. Khanji, M. Y.; Nolan, S.; Gwynne, S.; Pudney, D.; Ionescu, A. Tako-Tsubo Syndrome after Trastuzumab — an Unusual Complication of Chemotherapy for Breast Cancer. *Clinical Oncology* **2013**, *25* (5), 329–329. <https://doi.org/10.1016/j.clon.2012.12.007>.
49. Burgy, M.; Brossat, H.; Barthelemy, P.; Imperiale, A.; Trinh, A.; Hazam, C. A.; Bergerat, J.-P.; Mathelin, C. First Report of Trastuzumab Treatment after Postoperative Takotsubo Cardiomyopathy. *Anticancer research* **2014**, *34* (7), 3579–3582.
50. Lees, C.; Yazdan-Ashoori, P.; Jerzak, K. J.; Gandhi, S. Takotsubo Cardiomyopathy during Anti-HER2 Therapy for Metastatic Breast Cancer. *The Oncologist* **2018**, *24* (2), e80–e82. <https://doi.org/10.1634/theoncologist.2018-0285>.
51. Azzurra Irelli; Ceriello, L.; Patruno, L. V.; Tessitore, A.; Edoardo Alesse; Cannita, K.; Fabiani, D. Takotsubo Syndrome during Pertuzumab and Trastuzumab Therapy for HER2-Positive Metastatic Breast Cancer. *Biomedicines* **2024**, *12* (1), 179–179. <https://doi.org/10.3390/biomedicines12010179>.
52. Patel, V.; Tetyana Okan; Yee, J. L.; Patel, J. Trastuzumab-Induced Takotsubo Cardiomyopathy Leading to LV Thrombosis and Thromboembolic Stroke: A Case Report. *European Heart Journal - Case Reports* **2025**, *9* (2). <https://doi.org/10.1093/ehjcr/ytaf002>.
53. Numico, G.; Sicuro, M.; Silvestris, N.; Mozzicafreddo, A.; Trogu, A.; Malossi, A.; Cristofano, A.; Thiebat, B. Takotsubo Syndrome in a Patient Treated with Sunitinib for Renal Cancer. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology* **2012**, *30* (24), e218–20. <https://doi.org/10.1200/JCO.2012.42.4911>.
54. Ovadia, D.; Esquenazi, Y.; Bucay, M.; Bachier, C. R. Association between Takotsubo Cardiomyopathy and Axitinib: Case Report and Review of the Literature. *Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology* **2015**, *33* (1), e1–3. <https://doi.org/10.1200/JCO.2013.48.7280>.
55. Young Kwang Chae; Chiec, L.; Adney, S. K.; Waitzman, J. S.; Costa, R.; Carneiro, B. A.; Matsangou, M.; Agulnik, M.; Kopp, P.; Giles, F. Posterior Reversible Encephalopathy Syndrome and Takotsubo Cardiomyopathy Associated with Lenvatinib Therapy for Thyroid Cancer: A Case Report and Review. *Oncotarget* **2018**, *9* (46), 28281–28289. <https://doi.org/10.18632/oncotarget.25606>.
56. Fashafsha, Z.; Za, F.; Dy, S.; Df, M.; Es, T.; Aa, B.; Es, P.; Mg, P. *Annals of Clinical Case Reports Lenvatinib -Induced Takotsubo Syndrome in Patient with Thyroid Cancer OPEN ACCESS*; **2022**. <https://www.anncaserep.com/open-access/lenvatinib-ndash-induced-takotsubo-syndrome-in-patient-with-thyroid-cancer-9313.pdf> (accessed 2025-11-16).
57. Ramos, G. E.; Caglevic, C.; Bulnes, J. F.; Panay, S. E.; Zapata, M. I.; Daniele, A. J.; Rodríguez, M. E. Takotsubo Cardiomyopathy Afatinib-Related in a Non-Small Cell Lung Cancer Patient: Case Report. *Frontiers in cardiovascular medicine* **2022**, *9*, 1060813. <https://doi.org/10.3389/fcvm.2022.1060813>.
58. Giza, D. E.; Moudgil, R.; Lopez-Mattei, J.; Kim, P.; Iliescu, C. Association between Ibrutinib and Mid-Cavitary Takotsubo Cardiomyopathy: A Case Report and a Review of Chemotherapy-Induced Takotsubo's Cardiomyopathy. *European Heart Journal - Case Reports* **2017**, *1* (2). <https://doi.org/10.1093/ehjcr/ytx006>.

59. Tanaka, S.; Yagi, R.; Yoshimura, N.; Asakawa, R.; Ueno, K. Two Cases of Takotsubo Cardiomyopathy during Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment for Rare Non-Small Cell Lung Cancer with Epidermal Growth Factor Receptor Mutation EGFR遺伝子変異を有する稀な非小細胞肺癌に対してEGFR-TKI投与中にたこつぼ型心筋症が生じた2症例. *Haigan* **2024**, *64* (3), 200–205. <https://doi.org/10.2482/haigan.64.200>.
60. Trontzas, I. P.; Vathiotis, I. A.; Kyriakoulis, K. G.; Sofianidi, A.; Spyropoulou, Z.; Charpidou, A.; Kotteas, E. A.; Syrigos, K. N.; ImmunoTTS Collaborative Group. Takotsubo Cardiomyopathy in Cancer Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-Summary of Included Cases. *Cancers* **2023**, *15* (9), 2637. <https://doi.org/10.3390/cancers15092637>.
61. Zito, C.; Manganaro, R.; Ciappina, G.; Spagnolo, C. C.; Racanelli, V.; Santarpia, M.; Silvestris, N.; Carerj, S. Cardiotoxicity Induced by Immune Checkpoint Inhibitors: What a Cardio-Oncology Team Should Know and Do. *Cancers* **2022**, *14* (21), 5403. <https://doi.org/10.3390/cancers14215403>.
62. Geisler, B. P.; Raad, R. A.; Esaian, D.; Sharon, E.; Schwartz, D. A. Apical Ballooning and Cardiomyopathy in a Melanoma Patient Treated with Ipilimumab: A Case of Takotsubo-like Syndrome. *The Journal for ImmunoTherapy of Cancer* **2015**, *3* (1). <https://doi.org/10.1186/s40425-015-0048-2>.
63. Tan, N. Y. L.; Anavekar, N. S.; Wiley, B. M. Concomitant Myopericarditis and Takotsubo Syndrome Following Immune Checkpoint Inhibitor Therapy. *BMJ case reports* **2020**, *13* (9), e235265. <https://doi.org/10.1136/bcr-2020-235265>.
64. Yamada, K.; Mizuki Ida-Ichikawa; Fujimoto, N.; Ishida, M.; Kaoru Dohi. Takotsubo Syndrome in a Cancer Patient Treated with a Combination of Anti-Cancer Drugs Including Immune Checkpoint Inhibitors: A Case Report. *European Heart Journal - Case Reports* **2024**, *8* (8). <https://doi.org/10.1093/ehjcr/ytac355>.
65. Serzan, M.; Rapisuwon, S.; Krishnan, J.; Chang, I. C.; Barac, A. Takotsubo Cardiomyopathy Associated with Checkpoint Inhibitor Therapy: Endomyocardial Biopsy Provides Pathological Insights to Dual Diseases. *JACC: CardioOncology* **2021**, *3* (2), 330–334. <https://doi.org/10.1016/j.jaccao.2021.02.005>.
66. Malley, T.; Watson, E. A Case of Takotsubo Cardiomyopathy after Chemotherapy. *Oxford Medical Case Reports* **2016**, *2016* (4), 55–58. <https://doi.org/10.1093/omcr/omw014>.
67. Coen, M.; Rigamonti, F.; Roth, A.; Koessler, T. Chemotherapy-Induced Takotsubo Cardiomyopathy, a Case Report and Review of the Literature. *BMC Cancer* **2017**, *17* (1). <https://doi.org/10.1186/s12885-017-3384-4>.
68. Moldovan, B.; Adam, I.-I.; Radu-Mihai Pisciă; Vlad Untaru; Stolica, D.; Șpac, A.; Modrigan, I.; Ursu, M.; Jupoiu, L.; Frâncu, A.; Pescaru, F.; Amir Hubeishie; Zolog, A.; Vecerzan, L. Takotsubo Cardiomyopathy after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for a Recurrent Colon Cancer: A Life-Threatening Complication. *Diagnostics* **2024**, *14* (21), 2402–2402. <https://doi.org/10.3390/diagnostics14212402>.
69. Özbay, B.; Gürses, E.; Kemal, H. S.; Şimşek, E.; Kültürsay, H. Takotsubo Syndrome Early after Treatment due to Non Cardio-toxic Chemotherapy Agents. *Türk Kardiyoloji Dernegi arsivi : Turk Kardiyoloji Derneginin yayin organidir* **2021**, *49* (1), 72–75. <https://doi.org/10.5543/tkda.2020.25590>.
70. Pristipino, C. *Psychosomatic Medicine in Oncologic and Cardiac Disease Study (PSYCHONIC)*. Clinicaltrials.gov. <https://www.clinicaltrials.gov/study/NCT03437642> (accessed 2025-09-16).
71. Pelliccia, F.; Kaski, J. C.; Crea, F.; Camici, P. G. Pathophysiology of Takotsubo Syndrome. *Circulation* **2017**, *135* (24), 2426–2441. <https://doi.org/10.1161/circulationaha.116.027121>.
72. Wilkhoo, H. S.; Visvanathan, H.; Chatterjee, S.; Hussain, S.; Gundaniya, P.; Francis, V.; Singh, B.; Pillai, A. A. Current Clinical Perspectives on Takotsubo Syndrome: Comprehensive Analysis of Diagnosis, Management, and Pathophysiology. *International Journal of the Cardiovascular Academy* **2024**, *10*. <https://doi.org/10.4274/ijca.2024.63825>.
73. Arunachalam, K.; Gnanaguruparan, S.; Paulowski, J. Takotsubo Cardiomyopathy and LV Outflow Tract Obstruction after Initiation of Novel Oral Chemotherapy. *Rhode Island medical journal* (2013) **2020**, *103* (10), 40–43.
74. *The TAKO-TSUBO and Cancer Registry (TTAC)*. Clinicaltrials.gov. <https://www.clinicaltrials.gov/study/NCT01944826?cond=%22Broken%20Heart%20Syndrome%22&viewType=Table&rank=8> (accessed 2025-10-12).
75. Lyon, A. R.; Bossone, E.; Schneider, B.; Sechtem, U.; Citro, R.; Underwood, S. R.; Sheppard, M. N.; Figtree, G. A.; Parodi, G.; Akashi, Y. J.; Ruschitzka, F.; Filippatos, G.; Mebazaa, A.; Omerovic, E. Current State of Knowledge on Takotsubo Syndrome: A Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *European journal of heart failure* **2016**, *18* (1), 8–27. <https://doi.org/10.1002/ejhf.424>.
76. *Characterization of Primary and Secondary Stress Related Takotsubo (MAESTRO)*. Clinicaltrials.gov. <https://www.clinicaltrials.gov/study/NCT05793008?id=NCT05793008&rank=1> (accessed 2025-08-16).
77. *Psychosocial Support for Patients With Takotsubo Syndrome*. Clinicaltrials.gov. <https://www.clinicaltrials.gov/search?id=NCT05977049> (accessed 2025-10-02).
78. *EACVI Study on Multimodality Cardiovascular Imaging of Inflammatory Cardiovascular Diseases (EACVI-INFLAME)*. Clinicaltrials.gov. <https://www.clinicaltrials.gov/study/NCT07077304?id=NCT07077304&rank=1> (accessed 2025-09-16).
79. Adhikari, A.; Asdaq, S. M. B.; Al Hawaj, M. A.; Chakraborty, M.; Thapa, G.; Bhuyan, N. R.; Imran, M.; Alshammari, M. K.; Alshehri, M. M.; Harshan, A. A.; Alanazi, A.; Alhazmi, B. D.; Sreeharsha, N. Anticancer Drug-Induced Cardiotoxicity: Insights and Pharmacogenetics. *Pharmaceuticals (Basel, Switzerland)* **2021**, *14* (10), 970. <https://doi.org/10.3390/ph14100970>.
80. Zalewska-Adamiec, M.; Klonowska, P.; Małyszko, J.; Kuźma, Ł.; Bachorzewska-Gajewska, H.; Dobrzycki, S. Primary Takotsubo Syndrome as a Complication of Bladder Cancer Treatment in a 62-Year-Old Woman. *The American journal of case reports* **2021**, *22*, e930090. <https://doi.org/10.12659/AJCR.930090>.
81. Matsumoto, T.; Oda, T.; Yoshida, Y.; Kimura, S.; Hitomi Himi; Takao Tsuduki; Takagi, S.; Masahiro Takatani; Morishita, H. Takotsubo Cardiomyopathy Caused by Infusion Reaction to Trastuzumab. *International Cancer Conference Journal* **2019**, *9* (1), 28–31. <https://doi.org/10.1007/s13691-019-00396-0>.
82. Monti, M.; Cortesi, P.; Vespignani, R.; Ilaria Bronico; Gallio, C.; Flospergher, M.; Matteucci, L.; Giovanni Luca Frassinetti. Takotsubo Syndrome (TTS) in Onco-Hematologic Patients: Retrospective Analysis and Focus on the Correlation or Not with Anticancer Drugs. Case Reports and Review of the Literature. *Frontiers in Oncology* **2022**, *12*. <https://doi.org/10.3389/fonc.2022.875391>.
83. Fiste, O.; C. Trika; Syrigos, N. K.; Kotteas, E. A. A Rare Case of Takotsubo Cardiomyopathy. *PubMed* **2024**, *28* (5), 2063–2067. https://doi.org/10.26355/eurrev_202403_35619.
84. Taamallah, K.; Hela Ghedira; Younes Arous; Abdeddayem Hagui; Wafa Fehri. *Does emotion before a chemotherapy course break a heart? Cardiogenic shock complicating Takotsubo cardiomyopathy*. ResearchGate. <https://doi.org/10.21203/rs.3.rs-142578/v1>.

85. Khan, N. A. J.; Pacioles, T.; Alsharedi, M. Atypical Takotsubo Cardiomyopathy Secondary to Combination of Chemo-Immunotherapy in a Patient with Non-Small Cell Lung Cancer. *Cureus* **2020**, *12* (7), e9429. <https://doi.org/10.7759/cureus.9429>.
86. Stępień, K.; Nowak, K.; Pasieka, P.; Warmuz, K.; Stępień, A.; Nessler, J.; Zalewski, J. Typical Variant of Takotsubo Cardiomyopathy in Oncological Patients. Two Case Reports and Review of the Literature. *Folia medica Cracoviensia* **2020**, *60* (1), 45–54. <https://doi.org/10.24425/fmc.2020.133485>.
87. Goel, S. Chemotherapy-Induced Takotsubo Cardiomyopathy. *World Journal of Clinical Cases* **2014**, *2* (10), 565. <https://doi.org/10.12998/wjcc.v2.i10.565>.
88. Singh, S. B.; Harle, I. A. Takotsubo Cardiomyopathy Secondary in Part to Cancer-Related Pain Crisis: A Case Report. *Journal of Pain and Symptom Management* **2014**, *48* (1), 137–142. <https://doi.org/10.1016/j.jpainsymman.2013.09.002>.
89. Alekseev, I. E.; Lysovolenko, N. L.; Gavriluk, E. V.; Khvostovoi, V. V.; Lazareva, N. V.; Bykanova, A. M.; Grebenkin, E. N.; Stanoevich, I. V. Takotsubo Cardiomyopathy in Locally Advanced Rectosigmoid Junction Cancer: A Case Report. *Siberian journal of oncology* **2023**, *22* (5), 161–172. <https://doi.org/10.21294/1814-4861-2023-22-5-161-172>.
90. Ho, J. S. Y.; Ming Ng, T. Y.; Cen, S.; Sia, C.-H.; Chan, P.-F.; Yeo, T.-C. Metastatic Ovarian Cancer Presenting as Takotsubo Cardiomyopathy. *Heart and Mind* **2021**, *5* (2), 61–63. https://doi.org/10.4103/hm.hm_29_21.

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