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REVIEW

Unraveling Tumor-to-Tumor Metastasis: Insights into Pathogenesis, Diagnostic Challenges, and Treatment Modalities

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Abstract: Tumor-to-tumor metastasis (TTM) is defined as the metastasis of one distinct malignancy to another independent tumor without directly extending into the substance of a histologically distinct and separate tumor. TTM is an extremely rare phenomenon that constitutes a very small percentage of all tumor metastases. The detailed histogenic mechanisms of TTM remain unclear. TTM is easily confused with composite tumors and synchronous tumors. Due to the rarity and complexity of the disease, it presents significant challenges in providing accurate diagnoses and appropriate treatment options. The exploration of TTM not only provides an in-depth understanding of the metastasis process, but also has significant implications for the management and treatment of patients with multiple primary malignant tumors, underscoring the necessity of comprehensive diagnostic and treatment strategies. The purpose of this review is to increase awareness of tumor-to-tumor metastasis, with a focus on pathogenesis, diagnosis, and treatment.

Keywords: tumor-to-tumor metastasis, composite tumors, synchronous tumors, pathogenesis

Introduction

Tumor-to-tumor metastasis (TTM) is a rare yet fascinating phenomenon in which a metastatic tumor becomes the host for secondary metastasis from another primary tumor.[1] This unusual situation contrasts sharply with the more common scenario where cancer spreads to non-tumorous tissues or regional lymph nodes. Since both types of cancer exhibit high metastatic potential, this condition has been documented in various combinations.[2]

TTM was first described by Berent in 1902, and approximately 200 cases have since been reported. It accounts for a small fraction of metastatic cancers, with an estimated incidence of 0.1%. The increasing sensitivity of imaging techniques, such as PET-CT and advanced biopsies, has made it easier to detect previously undiagnosed metastases, contributing to rising detection rates. Additionally, broader cancer surveillance and earlier diagnoses have led to more frequent identification of multiple tumors, further increasing the recognition of TTM. However, due to its rarity and subtle presentation, TTM is often underreported or misdiagnosed as composite or synchronous tumors, complicating its accurate incidence assessment and potentially leading to incorrect treatment and management.

TTM can be classified into two types based on the origin of the metastatic tumor: donor and recipient. Previous studies indicated that certain types of tumors appearing more frequently in the role of either donor or recipient. The most frequent recipient is renal cell carcinoma due to its rich blood supply, which makes it a conducive site for metastases.[3] However, the thyroid gland, despite its rich blood supply, is a relatively uncommon site for metastases due to its unique physiological environment. Common donor tumors include lung cancer, breast cancer, and melanoma due to their high metastatic potential. But nowadays, there are more and more cases with renal cell carcinomas (RCC) as a donor tumor. Interestingly, when TTM occurs involving the thyroid, RCC is a frequent donor, highlighting the complex interplay of systemic factors and local tissue characteristics that influence metastatic behavior. The exact mechanism remains poorly

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understood, and uniform management guidelines do not yet exist. We reviewed the pathogenesis, diagnosis, and treatment of TTM, which aids in a better understanding and management of cancer patients.

The Pathogenesis of TTM

TTM is notable because both types of cancer have high metastatic potentials and specific pathophysiological characteristics that facilitate such rare events.[4] The pathogenesis underlying this phenomenon is likely multifactorial, and detailed mechanisms remain diverse without substantial proof. Although the physio-pathological mechanisms are not yet fully understood, there are several plausible theories to explain this phenomenon, including the "seed and soil" theory and the "Invasion-Metastasis Cascade".

The Seed and Soil Theory

The seed and soil theory posits that metastatic tumor cells thrive in conducive environments, similar to how seeds grow well in fertile soil. The most crucial elements are the "seed" (metastatic tumor cell) and the "soil" (hospitable environment). According to this theory, several factors can influence a neoplasm's ability to metastasize, including a rich vascular system and sufficient nutrition (Figure 1).

Seed (Donor Tumor Cell)

It is well understood that the potential of tumor cells to metastasize depends on their interaction with homeostatic factors that promote tumor growth, survival, angiogenesis, invasion, and metastasis. In the 1960s, Zeidman et al observed that some tumor cells were deformed and moved through narrow capillary tubes, while others, more rigid, were trapped. Of

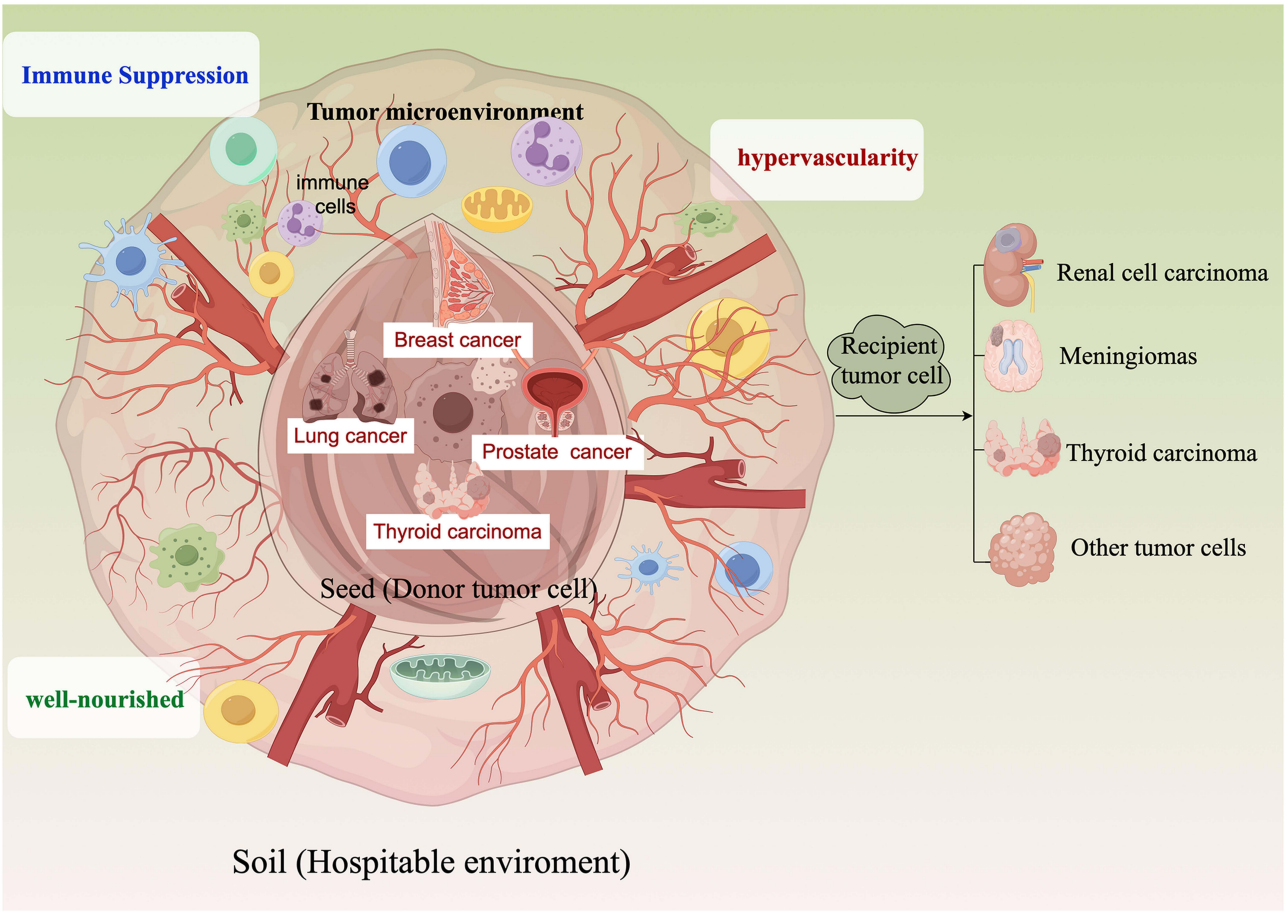

Figure 1 The seed and soil theory.

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the trapped cells, some produced metastases, but more died. Subsequently, researchers began labeling cancer cells with 125-iodo-deoxyuridine, which is embedded in DNA and thus remains within the cell. It was demonstrated that less than 0.1% of these cells remain viable within 24 hours of their release into the bloodstream, and less than 0.01% of those cells survive to form metastases when they enter the circulation.[5] Thus, only a small fraction of cells in a primary tumor can cause a metastasis. Therefore, metastasis may depend on either the fortuitous survival and growth of a very few neoplastic cells or the selective growth of unique subpopulations of malignant cells endowed with special properties.[6]

These profound results indicate that not all tumor cells can metastasize; only a select few are capable of achieving metastasis due to their genealogically and phenotypically unique subpopulations and properties. Moreover, each of these cells may have the potential to complete some steps in the metastatic process, but not necessarily all.

Soil (Hospitable Environment)

The formation of TTM is inseparably linked to the recipient, metastatic tumor cells, and their specific complex microenvironments. However, for a tumor to be a recipient in TTM, three conditions are required:[1] it must exhibit hypervascularity, enabling it to be affected by hematogenous metastasis;[2] it needs to be well-nourished, allowing donor tumor cells to grow; and[3] it should be characterized by slow growth and provide sufficient time for the development of the metastatic tumor cells from the donor. For instance, renal cell carcinoma is generally known for its hypervascularity and slow growth, making it a frequent recipient in TTM scenarios.

Due to the abundance of vasculature required by the recipient tumor, metabolic characteristics such as high collagen and lipid content may influence metastasis. Focal disruption of the blood-brain barrier by the recipient tumor, or immunocompromised patients with systemic diffusion of neoplasia, might also facilitate the spread of cancer cells.[7] In some cases, it has been observed that the tumor-suppressor gene of the recipient can be altered by the donor cell, thereby creating a more conducive environment for TTM.[8] This suggests that the outcome of metastasis is determined by the interaction between the metastatic cells and the homeostatic mechanisms, which the cancer cells can dominate. This is why TTM occurs. For example, meningiomas are the most common intracranial recipients for tumor-to-tumor metastasis, likely due to their slow growth and limited nutritive requirements, thus providing a sufficiently long period for metastatic seeding and a noncompetitive metabolic environment.

The Invasion-Metastasis Cascade

Scott Valastyan and Robert A. Weinberg proposed a new perspective on tumor metastasis in 2011, known as the "Invasion-Metastasis Cascade", with a focus on the primary tumor. According to their views, the primary tumors undergo a series of steps in the "Invasion-Metastasis Cascade to complete metastasis".[9] Thus, we have ample reason to suspect that TTM follows a similar process:[1] local invasion through the surrounding extracellular matrix (ECM) and stromal cell layers,[2] entry into the lumina of blood vessels,[3] survival during transport through the vasculature,[4] arrest at distant sites,[5] extravasation into the parenchyma of distant tissues, and[6] re-initiation of their proliferative programs at metastatic sites (recipient tumor), thereby generating macroscopic, clinically detectable neoplastic growths (Figure 2).

Similar to the seed and soil theory, for metastasis to occur, donor tumor cells must survive in a foreign microenvironment. The microenvironment at the transfer site is usually significantly different from that at the primary tumor formation site. This suggests that, at least initially, disseminated tumor cells require a suitable microenvironment. These microenvironmental differences may include the type of stromal cells, components of the extracellular matrix (ECM), available growth factors, and the microstructure of the recipient tumor itself. Meanwhile, one or more later stages of the invasion-metastasis cascade can only be successfully completed in very rare cases, which may also contribute to the low probability of TTM occurrence.

The Diagnosis of TTM

Diagnostic Criteria

The diagnosis of TTM is primarily based on histology and pathology. Pamphlett developed the following criteria for diagnosing tumor-to-tumor metastasis in 1984:[1] The metastatic nidus should be at least partly surrounded by a rim of histologically distinct primary tumor tissue;[2] the existence of a primary carcinoma must be proved; and[3] the metastatic

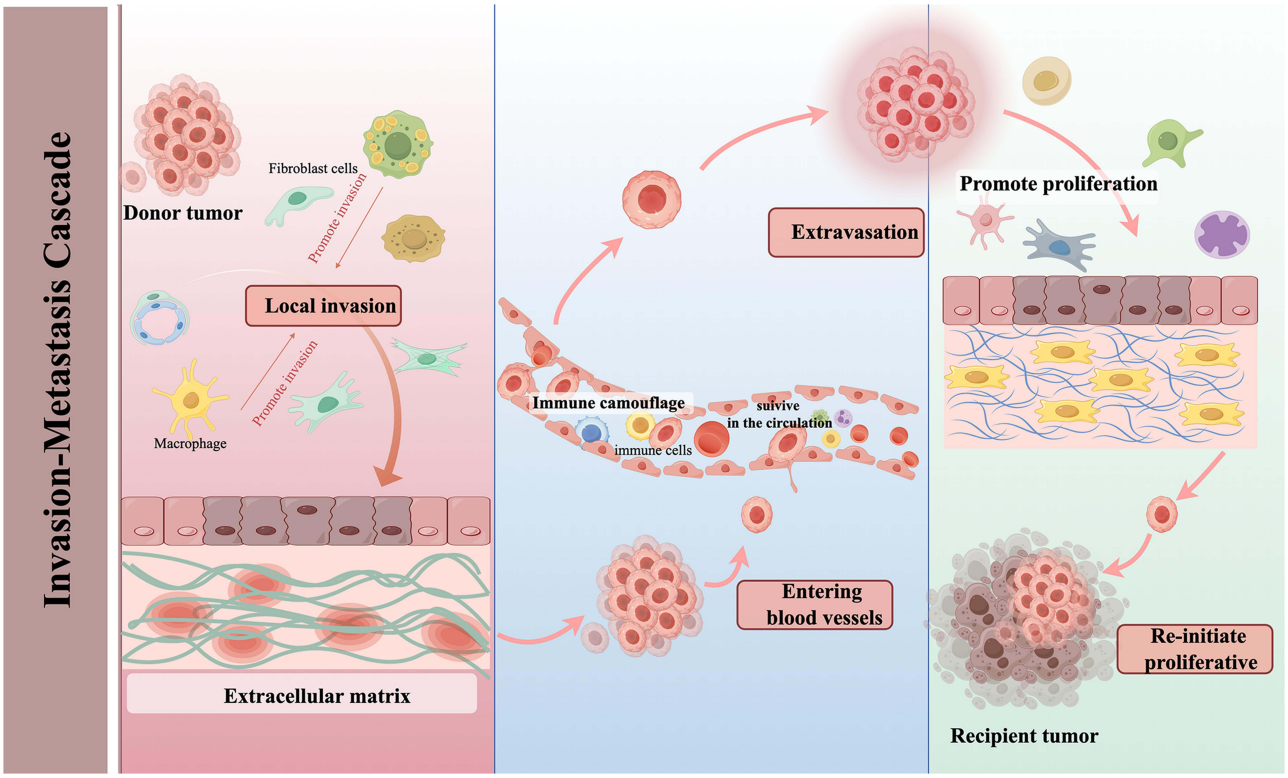

Figure 2 The Invasion-Metastasis Cascade of TTM.

tumor must be demonstrated as compatible with the primary carcinoma by morphological or immunohistochemical processes.[10] Dobbing and Campbell et al defined TTM using rigorous standards: when there are two or more distinct tumors, the recipient tumor must be a genuine tumor, and there must be a genuine metastasis in the tumor tissue of the recipient, in addition to the exclusion of lymphatic metastasis to lymphoma.[11] Thus, the coexistence of two tumors should be regarded as a complex condition, and it deserves to be treated with caution. Furthermore, TTM should be considered as a differential diagnosis for benign tumors that grow rapidly, even if malignancy is not initially confirmed by pathology.[8]

Differential Diagnosis

In clinical practice, it is important to differentiate TTM from collision tumors, composite tumors and synchronous tumors, as these concepts are often misunderstood or used interchangeably in the medical literature, leading to potential confusion.

Collision tumors are characterized by the presence of two distinct malignant neoplasms that meet and intermingle within the same organ but originate independently.[12] Each tumor retains its own characteristics and grows in close proximity to the other, without any metastatic spread from one to the other. The interaction involves proximity and mechanical intermingling rather than a true metastatic process. TTM involves the actual metastasis of cancer cells from a primary (donor) tumor to a distinct, pre-existing (recipient) tumor.[13] This process is unique because the recipient tumor serves as the metastatic site rather than normal tissues or organs, which are the more common targets for metastatic spread. This scenario implies a more dynamic interaction, where the secondary malignancy essentially becomes a host for metastatic cells from another, unrelated cancer.

A composite tumor is characterized by two distinct neoplastic components, which are morphologically and immunohistochemically different yet coexist closely within the same tissue mass.[14] The hallmark of composite tumors is not merely their proximity, but also the intermingling of these distinct cell types at the microscopic level. Often, they share

common genetic mutations that propel their growth, referred to as "driver mutations". For instance, the most frequently occurring renal composite tumor is the composite of papillary and RCC.[15]

Synchronous tumors are multiple primary tumors diagnosed simultaneously or within a relatively short period, typically within six months.[16] These tumors can appear in the same organ or in different organs. Genetic syndromes such as Lynch syndrome or familial adenomatous polyposis increase the risk of developing multiple cancers simultaneously or within a close timeframe.

Diagnostic Methods

Accurate diagnosis of TTM not only aids in understanding the patient's current disease state but also significantly influences the management strategy, impacting decisions on treatment modalities. Effective diagnosis involves a combination of imaging techniques, histopathological analysis, and sometimes molecular diagnostic tools. Assess the patient's history for previous malignancies which might suggest a source for the donor tumor. A tissue sample from the suspected recipient tumor is essential for a definitive diagnosis. Histopathological examination, utilizing special stains and markers, is crucial for identifying the primary tumor cells within a secondary tumor.

Molecular and genetic testing, such as Polymerase Chain Reaction, Fluorescence in Situ Hybridization (FISH), and next-generation sequencing (NGS) might be employed to analyze genetic differences between the tumors. These tests can help confirm if the cells from the suspected metastatic site genetically match those of a known or suspected primary donor tumor elsewhere in the body, especially useful in cases where histopathology is inconclusive. For example, a medical institution in China confirmed the diagnosis of a complex case of tumor metastasis from clear cell renal cell carcinoma to contralateral synchronous pheochromocytoma through FISH combined with NGS.[17]

Imaging, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) scans, may help identify multiple tumor sites, understand their nature, and determine the extent of metastasis. Positron Emission Tomography/Computed Tomography (PET/CT) scans offer the unique opportunity to provide not only whole-body images but also metabolic and functional information regarding tumor tissue, gradually becoming an emerging method for diagnosing tumors. Ghizlane Rais presented a case of clear cell renal cancer with metastasis originating from oligometastatic squamous cell lung cancer, detected in a PET/CT scan as part of an extension workup. This is the first PET/CT diagnosis of tumor-to-tumor metastasis (TTM).[18]

Projects like The Cancer Genome Atlas (TCGA) have revolutionized our understanding of the genomic foundations of various cancers. By mapping the genomes of numerous cancer types, these extensive collaborative networks have opened new avenues for diagnostics. Liquid biopsy, which detects circulating tumor cells and DNA that may originate from the primary tumor or microscopic metastatic foci, also plays a significant role in guiding the diagnosis of TTM. Recently, single-cell sequencing techniques, in conjunction with artificial intelligence, are being utilized in liquid biopsy to detect circulating tumor cells and predict tumor metastasis.[19]

The Treatment of TTM

Due to the extreme rarity of TTM, almost all clinical reports on this disease are case reports. To analyze optimal treatment strategies and prognosis, we reviewed all the literature published on PubMed and MEDLINE in the past five years. A total of 68 cases were identified using the keyword TTM from January 1, 2018, to December 31, 2023 (Table 1). Among them, female patients account for 60%, and more than 90% of patients are over 50 years old. Almost all patients were treated with surgical plans, some combined with radiotherapy, chemotherapy, immunotherapy, targeted therapy or hormone therapy. Regarding prognosis, it can be observed that the mortality rate of patients who received combined treatment with other therapies is only 8% lower than that of those who received surgical treatment alone. However, due to the small number of cases in the statistics, this does not fully explain the issue. Undoubtedly, the prognosis of the disease is related not only to the treatment plan but also to the types of tumors in the donor and recipient. Among the 68 cases studied, there were 18 deaths, with an equal number of recipients having benign and malignant tumors. Therefore, it is important to consider treating the primary donor tumor and early detection to prevent tumor metastasis as early as possible.

Table 1 The clinical characteristics, treatment, and prognosis of TTM cases from 2018 to 2023

Author and Year	Age	Sex	Donor Site	Recipient Site	Treatment	Clinical Outcome
Kolson Kokohaare et al (2018)[20]	NA	NA	Solitary Fibrous Tumor (malignant)	Thyroid Carcinoma (benign)	Surgery	NA
Karambizi et al (2018)[13]	61	Male	Lung adenocarcinoma (malignant)	Meningioma (benign)	Surgery	No recurrence
Grannan et al (2018)[21]	83	Male	Melanoma (malignant)	Oligodendroglioma (malignant)	Surgery, radiotherapy, immunotherapy, and chemotherapy	Died
Nan Liu et al (2018)[22]	70	Female	Lung adenocarcinoma (malignant)	Meningioma (benign)	Surgery	Died
Shuko Nomura et al (2018)[23]	71	Male	Gastric cancer (malignant)	Neck lipoma(benign)	Surgery and chemotherapy	Died
Jason T Pham et al (2018)[24]	64	Male	Lung adenocarcinoma (malignant)	Meningioma (benign)	Radiotherapy and chemotherapy	Lost to follow-up
Jason T Pham et al (2018)[24]	63	Female	Breast cancer (malignant)	Meningioma (benign)	Surgery, chemotherapy, and hormone therapy	Died
Ashraf Farrag et al (2018)[25]	57	Female	Breast cancer (malignant)	Meningioma (malignant)	Surgery, chemotherapy, and endocrine therapy	No recurrence
Andres Martin Acosta MD et al (2018)[26]	68	Male	Lung small cell carcinoma (malignant)	Meningeal melanoma (malignant)	surgery	NA
Osman Emre Aycan et al (2019)[27]	49	Female	Lung carcinoma (malignant)	Chondrosarcoma (malignant)	Surgery and chemotherapy	No recurrence in 6 weeks
Cavalcante et al (2019)[28]	80	Male	Prostate cancer (malignant)	Renal cell carcinoma (malignant)	surgery	No recurrence
Weiwei Tan et al (2019)[29]	35	Female	Breast carcinoma (malignant)	Pheochromocytoma (benign)	surgery	NA
Catherine F. Roy et al (2019)[30]	95	Female	Angiosarcoma (malignant)	Meningioma (benign)	NA	Died
Mitsutake Yano et al (2019)[31]	67	Female	Appendiceal adenocarcinoma (malignant)	Ovarian mature teratoma (malignant)	Surgery and chemotherapy	Died
Fioravanzo et al (2019)[32]	70	Male	Lung adenocarcinoma (malignant)	Glioblastoma (malignant)	Surgery	Died
Michael J. Yang et al (2019)[33]	59	Male	Hepatocellular carcinoma (malignant)	Vestibular Schwannoma (benign)	Surgery and chemotherapy	No recurrence
Shishido et al (2019)[34]	81	Female	Pulmonary carcinoid (malignant)	Solitary fibrous tumor (benign)	Surgery	No recurrence in 5 years

(*Continued*)

Table 1 (Continued).

Author and Year	Age	Sex	Donor Site	Recipient Site	Treatment	Clinical Outcome
Bertrand et al (2019)[35]	53	Female	Thyroid carcinoma (malignant)	Pulmonary carcinoid (malignant)	Surgery	NA
Ioana-Claudia Lakovschek et al (2019)[36]	79	Female	Breast cancer (malignant)	Renal cell carcinoma (malignant)	Surgery, radiotherapy and chemotherapy	Died
Yang Liu et al (2019)[37]	58	Female	Lung adenocarcinoma (malignant)	Fibrous histiocytoma (benign)	Surgery and chemotherapy	Died
Gang Wang et al (2019)[10]	74	Female	Breast carcinoma (malignant)	Squamous cell carcinoma of the bladder (malignant)	Chemoradiation	NA
X Xu et al (2019)[38]	49	Female	Primary insulinoma (malignant)	Hepatic adenoma (benign)	Surgery	NA
Fahoum et al (2020)[39]	80	Female	Colorectal adenocarcinoma (malignant)	Ovarian cyst adenofibroma (benign)	Surgery	NA
Sema Turker MD et al (2020)[40]	67	Female	Breast cancer (malignant)	Lung cancer (malignant)	Surgery, chemotherapy, and hormonal therapy	No recurrence in 19 months
Ayman Nada et al (2020)[41]	75	Male	Renal cell carcinoma (malignant)	Meningioma (benign)	Surgery and radiotherapy	NA
Sakai et al (2020)[42]	43	Female	Synovial sarcoma (malignant)	Uterine leiomyoma (benign)	Surgery	Synovial sarcoma recurrence after 26 months
Straker et al (2020)[43]	42	Male	Melanoma (malignant)	Thyroid carcinoma (benign)	Surgery	NA
Tianhao Hu, MD et al (2020)[44]	70	Male	Lung adenocarcinoma (malignant)	Meningioma (benign)	Surgery and hormonal therapy	Died
Christian Fernandez et al (2020)[45]	56	Female	Breast carcinoma (malignant)	Meningioma (benign)	Surgery, radiotherapy and chemotherapy	Died
Myoung Jae Kang et al (2020)[46]	52	Female	Breast carcinoma (malignant)	Lung adenocarcinoma (malignant)	Surgery	NA
Johannes Dietterle et al (2020)[47]	67	Female	Renal cell carcinoma (malignant)	Meningioma (benign)	Surgery, radiotherapy and hormonal therapy	No recurrence
Alexandros Psarris et al (2020)[48]	68	Female	Salivary gland adenocarcinoma (malignant)	Uterine leiomyoma (benign)	Surgery and chemotherapy	NA
Dayne Ashman et al (2020)[49]	57	Female	Breast carcinoma (malignant)	Renal cell carcinoma (malignant)	Surgery and chemotherapy	NA
Miriam Cieri et al (2021)[50]	52	Female	Renal cell carcinoma (malignant)	Gastric cancer (malignant)	Surgery and chemotherapy	NA

(*Continued*)

Table 1 (Continued).

Author and Year	Age	Sex	Donor Site	Recipient Site	Treatment	Clinical Outcome
Blagica Krsteska et al (2021)[51]	66	Male	Colorectal adenocarcinoma (malignant)	Renal cell carcinoma (malignant)	Surgery	Died
Diksha Karki et al (2021)[52]	27	Female	Sigmoid colon adenocarcinoma (malignant)	Uterine leiomyoma (benign)	Surgery	NA
Diana Caballero et al (2021)[53]	67	Male	Renal cell carcinoma (malignant)	Lung adenocarcinoma (malignant)	Surgery and chemotherapy	No recurrence
Uzair Jogiat et al (2021)[54]	70	Male	Esophageal adenocarcinoma (malignant)	Solitary fibrous tumor (benign)	Surgery and chemotherapy	No recurrence
Áurea Lima et al (2021)[55]	57	Female	Breast carcinoma (malignant)	Renal cell carcinoma (malignant)	Surgery and chemotherapy	NA
Benjamin Konstantinos Papadakis et al (2021)[56]	66	Female	Lung adenocarcinoma (malignant)	Meningioma (benign)	Surgery and chemotherapy	Died
Sat Prasad Nepal et al (2021)[57]	72	Male	Lung adenocarcinoma (malignant)	Renal cell carcinoma (malignant)	Untreated	Died
Kiziltan et al (2021)[58]	70	Female	Breast carcinoma (malignant)	Thyroid carcinoma (benign)	Surgery and chemotherapy	NA
Mohammad Hosseinzadeh et al (2021)[59]	60	Female	Breast carcinoma (malignant)	Meningioma (benign)	Surgery and chemotherapy	NA
Fatima Badawi et al (2022)[60]	63	Female	Renal cell carcinoma (malignant)	Thyroid carcinoma (benign)	Surgery	NA
Hsin-Yu Wen et al (2022)[17]	54	Female	Renal cell carcinoma (malignant)	Pheochromocytoma (benign)	Surgery and chemotherapy	No recurrence in the 6 months
Shunryo Minezaki et al (2022)[61]	72	Male	Renal cell carcinoma (malignant)	Pancreatic neuroendocrine tumor (malignant)	Surgery	No recurrence
Hiroki Natsui et al (2022)[62]	65	Female	Colon cancer (malignant)	Pancreatic neuroendocrine tumor (malignant)	Surgery	No recurrence in the 21 months
Ugolini Clara et al (2022)[63]	70	Male	Neuroendocrine tumors (malignant)	Papillary thyroid cancer (malignant)	Surgery	NA
Kelsey Martin et al (2022)[64]	75	Male	Renal cell carcinoma (malignant)	Lipoma (benign)	Surgery and chemotherapy	No recurrence
Ghizlane Rais, MD et al (2022)[18]	52	Male	Lung adenocarcinoma (malignant)	Renal cell carcinoma (malignant)	Surgery, radiotherapy and chemotherapy	Died

(*Continued*)

Table 1 (Continued).

Author and Year	Age	Sex	Donor Site	Recipient Site	Treatment	Clinical Outcome
Juan M. Colazo et al (2022)[65]	74	Male	Papillary thyroid cancer (malignant)	Nerve Sheath Tumor (benign)	Surgery	NA
R. Pirlog et al (2022)[66]	73	Male	Renal cell carcinoma (malignant)	Meningioma (benign)	Surgery	No recurrence in the 3 months
Loukas A. Georgiou et al (2023)[67]	**67**	Male	Lung cancer (malignant)	Meningioma (benign)	Radiotherapy, chemotherapy and immunotherapy	Died
Emma L. Short et al (2023)[68]	**73**	Male	Melanoma (malignant)	Angiofibroma (benign)	Surgery and radiotherapy	NA
Simone Furia et al (2023)[69]	**75**	Male	Thymoma (malignant)	Prostate Adenocarcinoma (malignant)	Surgery, chemotherapy, and hormonal therapy	NA
Woo Hyeong Joe et al (2023)[70]	**73**	Female	Breast carcinoma (malignant)	Meningioma (benign)	Surgery and chemotherapy	NA
Iisa Mansikka et al (2023)[71]	**69**	Female	Breast carcinoma (malignant)	Salivary gland tumors (malignant)	Surgery and chemotherapy	NA
Shiyue Liu et al (2023)[72]	**58**	Male	Prostate cancer (malignant)	Lung cancer (malignant)	Surgery, radiotherapy and chemotherapy	NA
Yusuke Sato et al (2023)[73]	**59**	Female	Follicular lymphoma (malignant)	Ovarian mature teratoma (benign)	Surgery	No recurrence in 12 months
Claudia Manini et al (2023)[74]	**67**	Female	Breast carcinoma (malignant)	Renal cell carcinoma (malignant)	Surgery	No recurrence
Claudia Manini et al (2023)[75]	**79**	Male	Renal cell carcinoma (malignant)	Meningioma (benign)	Surgery	No recurrence in 6 months
Claudia Manini et al (2023)[74]	**42**	Male	Renal cell carcinoma (malignant)	Papillary thyroid cancer (malignant)	Surgery	Died
Letian Zhang et al (2023)[75]	**66**	Female	Breast carcinoma (malignant)	Renal cell carcinoma (malignant)	Surgery, radiotherapy and chemotherapy	No recurrence
Michael Garneau et al (2023)[76]	**56**	Female	Lung adenocarcinoma (malignant)	Papillary thyroid cancer (malignant)	Surgery and chemotherapy	No recurrence in 5 years
Michael Garneau et al (2023)[76]	**76**	Female	Breast carcinoma (malignant)	Papillary thyroid cancer (malignant)	Surgery and chemotherapy	Metastasis to other tumors
Michael Garneau et al (2023)[76]	**54**	Female	Tonsillar squamous cell carcinoma (malignant)	Papillary thyroid cancer (malignant)	Surgery	NA
Michael Garneau et al (2023)[76]	**71**	Female	Neuroendocrine tumor (malignant)	Papillary thyroid cancer (malignant)	Surgery and radiotherapy	Died
Salman J Khan, et al (2023)[77]	**86**	Male	Colon carcinoma (malignant)	Meningioma (benign)	Surgery	NA

Abbrevition: NA, appliable.

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Generally, the prognosis of metastatic tumors is poor, with an even worse prognosis for TTM. However, in those with disseminated diseases, the overall survival rate of metastasis to the thyroid and other glandular organs (such as the adrenal glands, pancreas, and salivary glands) is better compared to other solid organs. As discovered in Table 1, complete resection of all metastatic diseases, regardless of organ site, improves cancer-specific survival rates compared to those without complete surgical resection.[78] However, even after surgery, the recurrence rate of tumors is high, with a relatively low 5-year survival rate. Therefore, to improve patient survival rates, a combination of various non-surgical treatment approaches is necessary. Non-surgical treatments mainly include chemotherapy and radiotherapy for patients who are not suitable for resection. In recent decades, treatment strategies have continuously innovated, utilizing advanced technologies such as whole exome sequencing, RNA sequencing, and single-cell sequencing to identify genetic characteristics and key molecules as potential therapeutic targets. Molecular targeted drugs that inhibit tumor growth, angiogenesis, and metastasis by targeting extracellular molecules such as vascular endothelial growth factor (VEGF), human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor (EGFR) have been successful in various clinical trials. Furthermore, recent breakthroughs in immunotherapy, such as tumor vaccines and immune checkpoint inhibitors, have brought hope for immunotherapy in TTM.[79] This promising approach may provide further treatment options for patients with metastatic diseases and bring hope to many in the future.

Surgical Treatment

Surgery is the primary treatment modality for TTM. A personalized comprehensive treatment plan is crucial, taking into account tumor type, location, the patient's overall condition, and potential complications. The goals of surgical treatment typically include alleviating symptoms, reducing tumor burden, and improving patient survival rates and quality of life. Definite preoperative diagnosis is crucial for developing treatment plans, as different types of tumors may require different approaches. Prior to surgery, detailed imaging studies and tissue biopsies are necessary to identify the type and location of the primary and metastatic tumors, enabling the formulation of personalized surgical plans. During the surgical procedure, surgeons must operate with caution to minimize damage to surrounding tissues, ensure complete tumor resection, and preserve the patient's function to the fullest extent. Postoperative follow-up and treatment are also crucial to monitor the patient's recovery and promptly address any complications. Due to TTM being a rare and complex phenomenon, treatment plans need to be individually tailored based on the specific circumstances of each case. Close collaboration among the surgical team, including neurosurgeons, pathologists, and radiologists, is essential to ensure the success of the surgery and a favorable prognosis for the patient.

In addition to traditional surgical treatment methods, innovative technologies such as the da Vinci robotic surgical system offer new perspectives for TTM surgical treatment. Unlike traditional laparoscopic surgery, robotic surgical systems provide surgeons with high-definition, three-dimensional visualization, improved flexibility, and operability, while minimizing hand tremors by achieving predetermined motion ratios and indexed movements.[80] Furthermore, with the advancement of molecular imaging technologies, near-infrared imaging has gradually been integrated into various surgical procedures. Near-infrared fluorescence navigation surgery (NIRF) includes fluorescent probes and imaging systems, with careful selection of suitable fluorescent probes being crucial for NIRF imaging. Indocyanine green (ICG) has become the most commonly used probe in NIRF and has been applied in various medical disciplines.[81]

Chemotherapy

Chemotherapy plays a crucial role in the systemic treatment of TTM. Multiple studies have emphasized the use of chemotherapy in managing cases of TTM. The selection of chemotherapy drugs is personalized based on the characteristics of the tumors, aiming to effectively suppress tumor growth and prevent further metastatic spread. For patients with TTM where either the donor or recipient tumor is benign while the other is malignant, administering a chemotherapy regimen targeting the malignant tumor is recommended. For example, in a case of rectal adenocarcinoma metastasizing to skull base meningioma, aggressive chemotherapy was used to treat neuroendocrine carcinoma.[82]

For patients with both donor and recipient tumors being malignant, priority should be given to treating the dominant tumor that impacts the patient's quality of life. In a case report involving diffuse large B-cell lymphoma metastasizing to gastric adenocarcinoma, the patient received six cycles of R-CHOP chemotherapy and achieved complete remission for

both tumors.[83] If the chemotherapeutic agents effective against both types of tumors are similar, a treatment regimen based on the effective chemotherapeutic agent can be chosen. For instance, oxaliplatin is the cornerstone chemotherapeutic agent for colorectal cancer, and the combination of gemcitabine and oxaliplatin is also a highly effective second-line treatment for lymphoma. Therefore, for patients with such TTM, a platinum-based chemotherapy regimen can be selected.

Radiotherapy

Radiotherapy is also one of the common treatment methods in TTM therapy. It can help reduce the size of the tumor or control its growth, alleviate local symptoms, and reduce the risk of recurrence. Compared to surgery, radiotherapy is a non-invasive treatment method suitable for cases where patients are not suitable for surgery. It can also be used in combination with surgery to achieve better treatment outcomes. In a case of breast cancer metastasis to the meninges, the rational use of radiotherapy can improve the patient survival rates.[45] Furthermore, advances in radiation biology emphasize the importance of understanding the different responses of various tumor types to radiation therapy. The effectiveness of radiation dose ranges and techniques may vary depending on the tissue involved, highlighting the necessity of personalized treatment approaches.[84]

Targeted Therapy and Hormone Therapy

Extensive research has explored the efficacy of targeted therapy in various types of cancer, emphasizing the inhibition of key molecular pathways associated with tumor cell growth, differentiation, migration, and angiogenesis.[85] In TTM, the recipient tumor and the donor tumor may share a common driver gene. HER2-positive breast cancer can be treated with HER2-targeted therapy in clinical practice. In lung adenocarcinoma, some patients also have HER2 gene mutations. This suggests that when HER2-positive breast cancer metastasizes to lung adenocarcinoma with HER2 mutation, HER2-targeted therapy may be effective for both tumors.

In certain tumors, such as breast cancer and prostate cancer, hormone overexpression can be treated with endocrine therapy. In a case of prostate cancer metastasized to the lung adenocarcinoma, the patient achieved good disease control with anti-androgen therapy combined with TKI inhibitors.[72]

Immunotherapy

The innate and adaptive immune systems are crucial for monitoring and eliminating non-self, mutated cells to maintain homeostasis and prevent tumor development and progression. However, these mutated cells can evade immune surveillance and rapidly proliferate through various mechanisms, including reducing the expression of major histocompatibility complex (MHC) molecules, blocking tumor antigens, and secreting immunosuppressive factors. Removing the immunosuppressive microenvironment of tumors is a new approach in cancer treatment, involving the use of immune checkpoint inhibitors, vaccines, and other immune modulators.[86] Programmed cell death ligand-1 is overexpressed on the surface of many tumor cells, suggesting that immune checkpoint inhibitors (ICIs) may have therapeutic potential in treating TTM. A recent study indicates that ICI plus chemotherapy achieves good disease control in a case of synchronous right upper lobe adenocarcinoma and left lower lobe squamous cell carcinoma.[87] Larsen et al also tried to treat an old patient with a complex case of malignant melanoma metastasizing to glioblastoma by combining surgical and chemo-radiotherapy options with pembrolizumab.[21] Although the addition of ICI did not improve clinical outcomes in some patients, it provided insights for the use of immunotherapy in TTM treatment.

Navigating the Management of TTM

The treatment of TTM requires a multidisciplinary team, including medical oncologists, surgical oncologists, radiation oncologists, and pathologists, to develop a comprehensive and individualized treatment plan. Identifying the types of tumors and their molecular characteristics is crucial because different cancers respond variably to treatments. Targeted therapy may be an option for tumors with shared driver mutations if suitable agents are available. If surgery is not contraindicated, maximal resection of the metastatic lesions is feasible. If the surgical margins are not negative, adjuvant radiation therapy may be considered postoperatively. Radiation therapy can also be a viable option for smaller lesions or those in critical areas that cause symptoms. Combined endocrine therapy may be considered for hormone receptor-

positive breast cancer or prostate cancer. Systemic chemotherapy is a feasible approach, regardless of the sensitivity of the recipient or donor tumor to chemotherapy. If both tumor types are sensitive to a specific class of chemotherapy agents, a regimen based on that agent may be chosen. Immune checkpoint inhibitors and other immunotherapies may be considered, especially if the tumors express specific antigens that the immune system can target. Additionally, patients with tumor-to-tumor metastasis may qualify for clinical trials exploring new treatment options or novel combinations of existing therapies.

Challenges and Future Perspectives

TTM is a rare and complex condition that presents significant challenges in both diagnosis and treatment. One of the main challenges in managing TTM is its diagnostic complexity. TTM often mimics other clinical conditions, making it difficult to differentiate from primary or metastatic lesions, and it is frequently underreported or misdiagnosed. Although imaging techniques such as PET-CT and MRI have improved detection, the lack of definitive biomarkers for TTM remains a major gap in clinical practice. This underscores the need for improved diagnostic strategies, including molecular profiling, advanced imaging techniques, and the development of TTM-specific biomarkers.

Treating TTM is another area that poses significant challenges. TM involves two different tumor types, each with distinct molecular profiles, making individualized treatment essential. Surgical resection is often the primary treatment when feasible, but responses to other therapies, such as chemotherapy, radiation, immunotherapy, and targeted treatments, vary depending on the characteristics of the recipient and donor tumors. The lack of clinical trials specifically addressing TTM further complicates the development of standardized treatment protocols. Research on the unique interactions between donor and recipient tumors, as well as the potential benefits of personalized treatments, is urgently needed.

The integration of emerging technologies in the study and management of TTM holds great promise. Liquid biopsy techniques, which enable the non-invasive detection of tumor markers in blood samples, could revolutionize TTM diagnosis by detecting metastases at earlier stages.[88] Single-cell sequencing provides an in-depth understanding of tumor heterogeneity, revealing the mechanisms that drive tumor-to-tumor spread and identifying potential targets for therapy. Furthermore, artificial intelligence is becoming increasingly valuable in oncology, offering more accurate diagnostic tools, predictive modeling, and personalized treatment strategies.[89,90] These technologies represent the future of TTM research and could significantly improve early detection and personalized therapeutic approaches.

Due to the rarity of TTM, collaborative research across institutions and disciplines is crucial for advancing knowledge in this field. Case reports, although often anecdotal, are essential for building evidence and refining diagnostic and therapeutic strategies. They provide real-world insights into the clinical presentation of TTM, highlighting diagnostic challenges, therapeutic responses, and potential impacts on patient outcomes. These reports not only enhance clinical understanding but also contribute to the development of evidence-based guidelines and protocols for managing TTM.

Looking ahead, research should focus on large-scale clinical trials and molecular studies to validate potential diagnostic biomarkers and treatment modalities for TTM. As understanding of the underlying biological mechanisms improves, developing more effective diagnostic tools, personalized treatments, and integrated therapeutic strategies will become more feasible. Additionally, increased awareness and education about TTM within the oncology community may improve early detection and lead to better outcomes for patients. The future of TTM research depends on overcoming diagnostic and therapeutic challenges through collaboration, technological innovation, and a deeper understanding of the underlying mechanisms. Addressing these challenges will improve the management of TTM and contribute to the broader field of cancer research, particularly in understanding tumor interactions and metastasis.

Conclusion

In conclusion, TTM is a complex phenomenon that presents significant challenges in oncology, requiring heightened awareness and advanced diagnostic strategies. The underlying mechanisms of TTM involve intricate biological interactions between different tumor types, including shared microenvironments, immune evasion, and specific molecular pathways that facilitate metastatic spread. Understanding these mechanisms is essential not only for accurate diagnosis but also for improving treatment outcomes.

Current treatment strategies for TTM must be highly individualized, taking into account the characteristics of both the recipient and donor tumors. Surgical resection remains a cornerstone of management when feasible, while adjuvant therapies such as radiation and systemic treatments tailored to the molecular profiles of the tumors offer further therapeutic options. The emerging roles of immunotherapy and targeted therapies in the management of TTM hold great promise, but require more focused research to fully understand their potential.

As we deepen our understanding of TTM, it is critical to emphasize the broader significance of these advancements. Collaborative research efforts are urgently needed to elucidate the mechanisms of TTM and to develop effective, standardized treatment protocols. These efforts not only hold the potential to improve patient outcomes for TTM but also to transform oncology practice as a whole, contributing to the evolving landscape of cancer treatment. Future studies, particularly large-scale clinical trials and molecular research, will be crucial in establishing standardized diagnostic and treatment approaches for TTM, ultimately enhancing the management of this rare yet clinically important phenomenon.

Data Sharing Statement

The data supporting the conclusions of this manuscript will be made available by the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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