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Treatment-induced brain tissue necrosis: a clinical challenge in neuro-oncology

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Abstract

Cancer therapy-induced adverse effects on the brain are a major challenge in neuro-oncology. Brain tissue necrosis (treatment necrosis [TN]) as a consequence of brain directed cancer therapy remains an insufficiently characterized condition with diagnostic and therapeutic difficulties and is frequently associated with significant patient morbidity.

A better understanding of the underlying mechanisms, improvement of diagnostic tools, development of preventive strategies, and implementation of evidence-based therapeutic practices are pivotal to improve patient management. In this comprehensive review, we address existing challenges associated with current TN-related clinical and research practices and highlight unanswered questions and areas in need of further research with the ultimate goal to improve management of patients affected by this important neuro-oncological condition.

Keywords

complications | malignant glioma | radiation necrosis | treatment effects | treatment necrosis

Cancer treatment-related effects on the central nervous system remain a challenging issue in neuro-oncology.[1,2] Specifically, treatment-induced brain tissue necrosis (treatment necrosis [TN]), perhaps inappropriately referred to as "radiation necrosis," continues to be a challenge for clinical management and can be a significant cause of patient morbidity and even mortality.[3–6] Radiographic and clinical presentation of TN is usually indistinguishable from those of residual/recurrent tumor (progressive disease [PD]), causing a major dilemma in patient management. Establishing a reliable diagnosis based on clinical assessment and conventional MRI is difficult, frequently necessitating a surgical tissue biopsy.[1,2,5,7] The pathophysiology of TN is complex and incompletely understood.[8,9] Depending on the location and extent of the necrotic lesion and the degree of associated mass effect, the condition's clinical course may be heterogeneous and unpredictable.[5] To date, no standard of care (SOC) for TN exists and treatment is mostly directed at controlling associated neurological symptoms.[5] Experimental therapies have shown mixed efficacy and await robust evidence-based assessment[5,10]; a consensus regarding best practices for efficient preventative, diagnostic, and therapeutic measures to manage TN has not yet been established.[5,11]

This review discusses diagnostic and therapeutic strategies directed at management of patients with TN, focusing on clinical pitfalls and research barriers that have precluded advancement of this field. Of note, the term "treatment (-induced) necrosis (TN)"[12–14] (unlike the conventional clinical term "radiation necrosis") reflects emerging knowledge of the mechanisms driving this condition. Specifically, existing studies point to a contribution of chemotherapeutic agents such as temozolomide (TMZ)[13] or tyrosine kinase inhibitors[15] and pre-existing comorbidities to the development of TN.

Treatment-Induced Necrosis: A Clinical Challenge

Our observations and those of others[1,2,5,12–14,16–22] suggest that numerous clinical and systemic factors complicate the understanding and management of TN, as summarized in Fig. 1. Addressing these challenges is essential to define risk factors and preventative strategies, reliable diagnostic and monitoring algorithms, and effective patient management practices.

Incidence and Clinical Relevance

TN constitutes a serious and relatively common treatment-related adverse effect, particularly since combined chemotherapy and radiation therapy (RT) with concurrent and sequential TMZ[23] was established as the SOC treatment for glioblastoma (GBM).[13,14,17] The exact incidence and prevalence of TN remains unknown; depending on the type of neoplastic lesion, treatment regimen, and data acquisition parameters, TN incidence ranges from 3–24%[9,24] or 5–50%.[8,25] For high-grade glioma patients, Ruben et al reported a 4.9% incidence of TN following RT (± adjuvant chemotherapy).[24] However, this study was not fully biopsy-controlled and patient data derived from an era before standard chemo-RT[23] was implemented. Since then, Chamberlain et al[13] found a 14% incidence of biopsy-confirmed TN in TMZ-based chemo-RT treated GBM patients, supporting the notion that the incidence with combined chemo-RT may be higher. Any improvement of patient overall survival (OS) with use of novel anti-neoplastic treatments will likely be associated with an increase in TN manifestation.[4] Moreover, the incidence and severity of TN is influenced by the choice of treatment modality, including targeted therapies, immunotherapies, anti-angiogenic therapies, and concurrent steroid use. For instance, TN incidences may be higher in patients treated for brain metastasis with tyrosine kinase inhibitors[15] and lower in those concurrently treated with corticosteroids[26] and anti-angiogenic therapies.[27,28] Whether immune checkpoint inhibitors may increase the risk of TN in patients with metastatic brain cancer has been discussed controversially.[29,30]

Risk Factors and Prevention

Prevention of TN is limited by an incomplete understanding of risk factors and a lack of efficacious neuroprotective strategies. Apart from anti-neoplastic treatment parameters, such as RT type (eg, brachytherapy, stereotactic radiosurgery) and radiation modality (proton vs photon radiation), radiation dose, -volume, -fraction size and/or hyperfractionation regimen, and use of concurrent and/or adjuvant chemotherapy, other potential risk factors for TN include patient age, survival time, and vascular comorbidities.[7,10,14,24,31–34] However, poor predictability and heterogeneity of TN suggest that additional yet unidentified risk factors are implicated.[35]

Radiographic Appearance and Spatiotemporal Pattern

Lacking a distinctive radiographic signature, TN is mostly indistinguishable from PD on conventional structural MRI.[2,7,14] As such, TN commonly occurs in close proximity to the original tumor location, usually appearing as a focal (or multiple) contrast enhancing nodule(s) with associated T2/fluid attenuated inversion recovery signal hyperintensity consistent with perilesional vasogenic edema[1,2,7] (Fig. 2). While thought to occur most commonly at the site of maximum radiation exposure (ie, adjacent to the tumor or surgical resection cavity),[7,14,17] a detailed correlative analysis of the spatial pattern of TN with the radiation field has, to our knowledge, not yet been carried out. Interestingly, solitary or multiple de novo necrotic lesions can also occur more remotely, on ipsilateral or even contralateral cerebral hemispheres.[7]

The periventricular white matter is considered a predilection site for TN, likely due to its high susceptibility to radiation-induced microvascular injury.[7,14,36] Some have observed a high frequency of corpus callosum involvement and subependymal expansion with TN as opposed to PD,[16,37] although the opposite was observed by others.[38] Further distinct MRI features of radionecrotic lesions, such as a "Swiss cheese" or "soap bubble"–like interior enhancement,[7] a "spreading wavefront" pattern of the lesion,[38] or a radiographic lesion quotient,[39] have been put forward. Despite these efforts, authoritative diagnosis of the condition based solely on conventional MRI has remained largely elusive.[14] Lastly, the frequent presence of "mixed" brain lesions, consisting of both TN and residual and/or recurrent (necrotic) tumor,[7,38,39] causes additional ambiguity on conventional MRI, making it a poor diagnostic tool for TN.

The temporal manifestation pattern of TN is highly variable.[5] While late-delayed radiation injury—predominantly manifesting as TN—frequently occurs within 12 months post-RT,[5,17,40] TN may develop months to many years after treatment, occasionally occurring up to a decade later.[3,41] Recent findings point to an increasing appearance of "early necrosis" developing within the first 6 months post-RT in those patients with glioma who receive standard chemo-RT, suggesting that concurrent TMZ may act as a radiosensitizing agent.[13] In this context, it has been hypothesized that (early) TN manifestation might serve as a predictive biomarker for a more durable treatment response.[13,17] This assumption should be interpreted with caution, as survival analyses carried out in patients with treatment-related effects are inherently reflective of a selected patient population with an implicit time bias, which needs to be accounted for.[36]

Finally, the distinction between different types of treatment-related effects is the subject of active clinical debate.[5] Apart from TN, other less severe and usually more transient types of treatment-related effects include acute and early-delayed radiation injury,[3,8,41] as well as pseudoprogression (PP).[1,14] While these entities are primarily distinguished by differences in temporal and clinical patterns, they are somewhat arbitrarily defined and may occasionally overlap, creating diagnostic ambiguities (Fig. 3).[5] In particular, the delineation between PP and TN has been complicated by semantic inconsistencies regarding the meaning of the term "pseudoprogression." PP likely

Clinical factors	Identified core issues
Risk factor profile	• Insufficient characterization; likely complex dynamic interplay between unknown predisposing *intrinsic* factors (patient clinical status, inherent genetic susceptibility, tumor entity & molecular-genetic factors) and partly identified *extrinsic* factors (treatment regimen).
Complex pathomechanisms	• Incomplete understanding of causal sequence of events and key targetable pathways/molecules driving & sustaining TN.[8,9]
Spatio-temporal radiographic pattern	• Incoherent terminology /arbitrary temporal distinction between pseudoprogression (PP), vs early-delayed radiation injury vs "early necrosis" vs TN. • Lack of spatial analyses correlating anatomical location of TN lesions with therapeutic radiation dose distribution and respective Rx dose exposure.
Mixed lesions	• Frequent manifestation of lesions containing both TN and residual or recurrent tumor and/or tumor necrosis.[7,38] Inability to distinguish between mixed entities on conventional MRI → pitfall for identifying correct biopsy targets, affecting diagnostic yield.
Diagnostic ambiguity *Radiographic*	• Inability to distinguish TN from PD on conventional MRI → no optimal advanced imaging modality → lack of robust imaging biomarkers → no consensus on preferred non-invasive diagnostic algorithm.[2,5,7] • Concomitant treatment with glucocorticoids, anti-angiogenics, or immune/targeted therapies may further complicate image interpretation with conventional MRI.[10,21,42]
Clinical	• The clinical picture of TN frequently mimics that of PD.[5]
Histopathological	• No established histopathological classification criteria for TN or PP → final pathologic diagnosis largely depends on pathologist's experience and subjective impression. • Radiation induced cellular atypia in non-neoplastic cells may mimic intra-lesional infiltration by scattered tumor cells and these can be virtually indistinguishable.[6]
Clinical course	• Heterogenous, difficult to predict. • Symptomatic cases may further progress or deteriorate despite medical intervention, occasionally requiring surgeryto prevent fatal outcome.[2,5] • Lack of level I or II clinical evidence for currently available treatment options.
Systemic factors	**Identified core issues**
Prospective biopsy-controlled studies	• There is a paucity of both prospective and biopsy-controlled studies that assess the predictive value of advanced diagnostic imaging methods for TN.[19] • Conversely, routine biopsy of diagnostically ambiguous casescarries surgical risk, may curtail patients' quality of life (QoL), and is associated with increased costs.
Focused randomized controlled clinical trials (RCTs)	• Lack of RCTs with endpoints devoted to characterizing treatment effects. • Potential "treatment effect confounders" are insufficiently controlled for in past and ongoing clinical trials → pitfall to interpretation of efficacy of experimental anti-neoplastic agents.[13,21,22]
Functional imaging performance assessment	• Poor inter-study comparability of diagnostic performance of functional imaging modalities due to associated image-acquisition/processing standardization issues.[16]
Clinical feasibility of functional imaging	• No comprehensive availability of advanced imaging modalities in standard medical care facilities.[12] • Increased operating cost of scanners/equipment, lack of insurance coverage for advanced diagnostic procedures.[12] • Frequent diagnostic need to combine different modalities → increased cost and time
Response assessment criteria	• Insufficiency of current criteria in accounting for potential radiographic correlates of treatment effects in follow-up treatment response monitoring
Current diagnostic approach	• Risk of over-emphasis on radiologic findings → pitfall of excluding potentially important risk factors, antecedent events and clinical aspects that may corroborate or challenge a Dx of TN.

Fig. 1 Overview of clinical and systemic factors challenging the study and better understanding of TN. Dx = diagnosis; QoL = quality of life; Rx = radiation.

represents a unique, transient scenario in patients with high-grade glioma within the first 3 months of combined TMZ-based chemo-RT.[1] Recently, van West et al employed this term to describe late enhancing, treatment-related lesions (median onset 12 mo post-RT) they observed and characterized in patients with low-grade glioma.[36] Concluding that the delayed onset for these lesions differed clearly from the earlier timeframe for PP in patients with high-grade gliomas, the authors suggest that these lesions "could be small areas of radiation necrosis."[36]

Diagnostic Considerations

Defining a reliable diagnostic algorithm for accurate detection of TN has been hampered by its radiographic similarity to PD on conventional MRI[2,7] and frequent manifestation as a mixed pathology with recurrent or residual tumor.[7,39] Moreover, complex radiographic findings seen after combinatorial anti-angiogenic, cytotoxic, and immunotherapy regimens[21,42,43] compromise adequate MRI-based follow-up monitoring and characterization of treatment response with Macdonald and revised Response

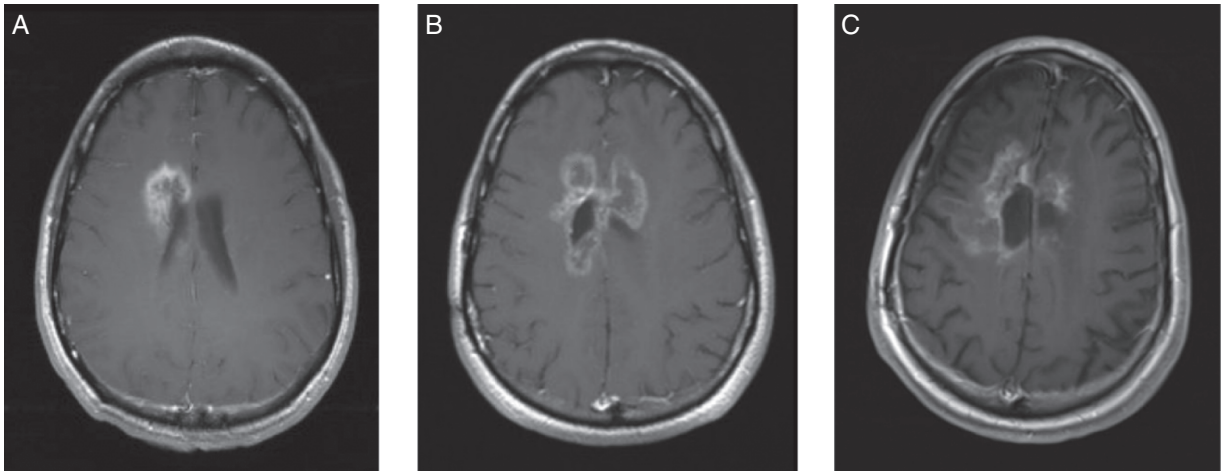

Fig. 2 Progressive treatment necrosis (A–C; T1-weighted gadolinium-enhanced axial MRI sequences). (A) A 35-year-old male with right frontal low-grade astrocytoma (World Health Organization grade II) underwent surgical resection followed by TMZ-based chemo-RT treatment. Eight months post-RT completion he developed headaches of increased frequency and was found to have a new nodular focus of enhancement in the right frontal lobe subjacent to the resection cavity, with periventricular and corpus callosum involvement, a biopsy of which revealed TN. (B) Sequential TMZ was resumed and completed over the next 6 months; however, the patient experienced worsening of his symptoms as the region of enhancement continued to expand. (C) Despite initiation of corticosteroid and bevacizumab treatment, he developed progressive left-sided hemiparesis and cognitive decline over the following 2 years, prompting a second biopsy of the continually enhancing lesion, which again confirmed TN. Therapeutic management of symptomatic TN was continued; however, the patient deteriorated further, necessitating a transfer to hospice care, where he eventually passed away 2 years after the second biopsy.

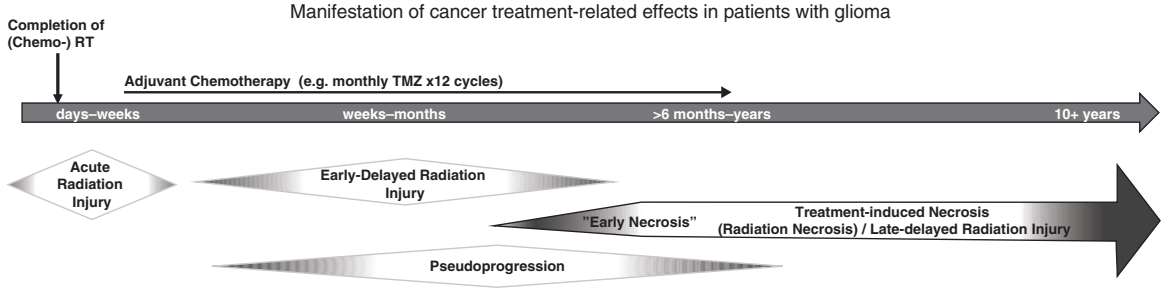

Fig. 3 Timeline schematic illustrating the temporal manifestation pattern and clinical course of cancer treatment–related effects. Acute and early-delayed types of radiation injury represent transient, reversible neurotoxic phenomena observed within days to weeks, and weeks to several months following chemo-RT.[41] By contrast, TN typically constitutes a late-delayed type of radiation injury observed >6 months post-RT with a frequently irreversible and progressive course[1]; however, concurrent TMZ-based chemo-RT may contribute to increasing incidences of "early necrosis."[13] Pseudoprogression (PP) likely represents a unique, transient, predominantly radiographic phenomenon encountered in patients with high-grade glioma within the first 3 months of combined TMZ-based chemo-RT.[1] Differentiation between these entities remains a clinical challenge.

Assessment in Neuro-Oncology (RANO) criteria.[44–46] While existing RANO criteria limit clinical trial enrollment to patients with radiographic PD in whom contrast enhancing lesions appear at or beyond 12 weeks post-RT,[46] treatment-related effects (especially TN) frequently manifest beyond this cutoff point (Fig. 3). Misdiagnosis of tumor progression could result in premature first-line treatment discontinuation and administration of a salvage treatment (which should have been withheld until true PD) or may delay a necessary treatment change in cases where treatment effects, such as PP or TN, are mistakenly assumed.[20,22,44] Furthermore, erroneous inclusion of misdiagnosed patients into clinical trials condones misinterpretation of the efficacy of any investigational agent.[13,21,22]

Beyond efforts to revise currently employed radiographic treatment response assessment criteria,[18,21] attempts to identify more accurate, clinically feasible diagnostic imaging biomarkers and, ultimately, enable a "virtual biopsy" of TN[1,12,17,40] have included the assessment of diffusion weighted[47] and diffusion tensor[48] MRI, MRI perfusion studies,[49–51] CT perfusion (CTP) studies,[52] MR spectroscopy (MRS),[53–55] positron emission tomography (PET),[56–59] single photon emission computed tomography (SPECT),[60] or combinations thereof.[55,61,62] Notwithstanding, histopathological evaluation remains the diagnostic gold standard,[5,11] albeit many of the aforementioned non-invasive technologies hold substantial additive value in complementing conventional MRI findings and improving diagnostic certainty in cases of suspected TN and when a surgical tissue biopsy is too risky or otherwise not feasible.[1,12,17,19,20,40] Further advantages include guidance for stereotactic biopsy procedures and more tailored, less neurotoxic radiation field mapping for radiotherapeutic interventions[16] (eg, via quantitative TN versus PD distinction within mixed lesions), identification of tumor "hot spots," and characterization of the degree of tumor infiltration into perilesional brain parenchyma. Techniques such as MRI-localized biopsies and radiographic-histopathological correlations (eg, via MR signal intensity to cell density correlation maps)[63] have addressed the challenges of tumor sampling resulting from the high degree of intratumoral heterogeneity and frequent presence of mixed pathology following anti-neoplastic treatment.

Several reviews have evaluated the growing body of literature on the role of advanced imaging in TN diagnosis.[12,16,19,20,40,64] Concluding that a preferred non-invasive diagnostic gold standard for TN is still lacking, several reports identify distinct strengths and weaknesses of various imaging modalities, and provide valuable recommendations for clinical practice and research design (Table 1). Methodological problems involve the lack of randomized controlled clinical trials, absence of histopathological verification of lesions identified by imaging, poorly matched patient groups, high variability in clinical practices at time of radiographic disease progression, and potential operator dependency in radiographic assessment.[12,19,20,64] Moreover, most studies investigate a single imaging modality, whereas combined use of multiple functional imaging modalities has become a common clinical reality with improved diagnostic accuracy.[12,20,55,62] Other difficulties relate to producing methodologically accurate meta-analyses of published data due to inconsistencies in defining TN[40] and unresolved standardization in image acquisition and processing.[16]

Most reviews emphasize a critical necessity for prospective, biopsy-controlled studies to improve the current body of evidence.[12,19,20,64] Moreover, widespread adoption of advanced imaging is difficult to achieve in clinical practice due to limited availability, high operational costs, and common lack of insurance coverage for such procedures.[12] Low spatial resolution of most techniques and limited utility for accurate longitudinal monitoring (due to standardization issues) are additional concerns.[16]

Recommendations on diagnostic imaging for TN versus PD distinction vary. Several groups endorse multivoxel MRS,[19,20,65] PET with novel amino acid based radiotracers,[19] (technetium-99) SPECT,[20,40] and CTP.[16,40] Conversely, routine diagnostic use of fluorodeoxyglucose (^{18}F-FDG) PET is discouraged due to its low specificity and poor signal-to-noise ratio.[20,40] Nevertheless, virtually all neuroimaging techniques were found to bear some specific disadvantages (see Table 1). Others have therefore advocated a multimodal diagnostic approach through the combined use of several techniques,[12] such as MRS with diffusion-weighted imaging (DWI),[55] or MRI combined with fluoro-ethyl-tyrosine (FET) PET and MRS.[62] The advent of hybrid PET-MRI[56] may facilitate such combinatorial approaches in becoming more clinically feasible and less time-consuming.[18] An interesting novel approach includes the use of delayed-contrast MRI to construct treatment response assessment maps (TRAMs) for differentiation of PD from treatment effects based on delayed contrast accumulation (nontumor tissues) versus contrast clearance (representing active tumor).[66] Histological validation demonstrated 100% sensitivity and 92% positive predictive value to active tumor of this approach, including adequate representation of tumor burden by TRAMs.

Blood-based biomarkers are increasingly explored for diagnosis and treatment response in neuro-oncology, including efforts to achieve liquid biopsy-based differentiation of treatment effects from PD, with technical limitations mainly pertaining to sensitivity issues.[67] One recent study investigated expression profile differences of myeloid-derived suppressor cells (MDSCs) as a potential biomarker for predicting recurrent GBM and differentiating it from TN.[68] While early results of this approach have been encouraging, potential diagnostic feasibility of the MDSC biomarker for lower-grade gliomas—where TN would be expected to occur even more frequently—remains to be established. The predictive value of this approach in the setting of "mixed lesions" remains unclear, as only TN lesions with <5% of active tumor were included.[68] Other previous efforts have investigated blood-derived microvesicles as a potential diagnostic biomarker for PD versus TN/PP differentiation in chemo-RT treated GBM patients with equivocal imaging findings.[69]

Finally, histopathological diagnosis and classification of biopsied lesions raises several challenges. Currently, no specific guidelines for histopathological characterization of treatment-induced brain tissue necrosis or other treatment-related effects exist; the final pathological diagnosis depends largely on the pathologist's professional

Table 1 Comprehensive overview of existing reviews assessing the diagnostic performance of different advanced imaging modalities for TN vs PD

Study/Type	No./Types of Studies Reviewed	Selected Notable Findings	Key Issues Identified	Overall Recommendations
Alexiou et al, (2009)[19] **- Systematic Review** **- Focus on value of MRI techniques, SPECT, PET to differentiate TN from glioma recurrence.**	46 clinical studies - 3 Class I, - 9 Class III, - and 34 Class IV evidence level studies	*DWI / MRS:* several Class III & IV studies. - 1 biopsy-controlled Class I study (Rock et al, 2004) showing MRS ratios (Cho/NAA, NAA/normal Cr and NAA/Cho) can reliably differentiate TN from PD. ADC values improved differentiation, but not in mixed lesions. *PET:* majority Class III & IV studies. - Accuracy of ^{18}F-FDG-PET hampered by high background signal; ranges of 62–100% sensitivity and 40–100% specificity in evaluated studies. - Novel PET tracers (^{11}C-MET,^{18}F-FDOPA,^{18} F-FET) with different advantage/ disadvantage profiles, but potentially improved diagnostic sensitivity (75–100%) and specificity (75–100%). - 1 prospective biopsy-controlled study (Mehrkens et al, 2008) showed 84% pos. predictive value of ^{18}F-FET PET for detecting glioma recurrence.	- Majority of studies had ↓evidence levels - Many studies not biopsy-controlled - Mostly retrospective design - Unclear methodology in some studies	- Tentative recommendation to use multivoxel MRS and/or PET with newer radiotracers to detect true tumor recurrence - Recommendation to carry out prospective, biopsy-confirmed studies with higher evidence levels.
Jain et al, (2010)[16] **- Comprehensive Review** **- Discusses individual advantages, limitations, and clinical utility of functional neuro-imaging modalities in distinguishing between TN and PD.**	Unspecified number of key studies discussed: - Perfusion imaging studies - MRS studies - DWI/DTI studies - PET/SPECT studies	*Perfusion imaging:* limited performance in mixed lesions and in pat. receiving anti-angiogenic treatments. - Potential advantage of CTP over MR perfusion, due to relative ease to generate quantitative perfusion parametric maps through defined arterial input & venous output function. - CTP clinical utility limited by Rx exposure + iodinated contrast agent; MR perfusion easily obtainable as additional sequence to conventional Gd-MRI. - 1 biopsy-controlled CTP study showed 83.3% sensitivity / 100% specificity for TN vs PD detection (Jain et al, 2007) *MRS:* most studies lack biopsy-controls. - MRS metabolic ratios can reliably differentiate pure, but not mixed lesions with tissue heterogeneities below current spatial resolution (~1 cc). - Multivoxel > single voxel MRS for diagnostic performance (Chernov et al, 2005) - Longer scan times required to obtain reproducible data. *DWI*: Unresolved ongoing discussion on which lesion type (TN or PD) has higher ADC values. *PET / SPECT*: Overall more limited availability and ↓spatial resolution - ^{18}F-FDG-PET downsides: ↑background signal, potential false-negatives (LGG appear hypometabolic) or false-positives (abscess or reactively inflamed TN lesions can appear hypermetabolic). - These challenges might be improved by employing novel amino acid tracers or combinations thereof with FDG, as well as co-registration of PET with structural MRI.	- Most techniques lack standardization of image acquisition & post-processing parameters → 1) difficulty to use as treatment response monitoring tool. 2) difficulty to conduct multicenter studies or compare different studies. - Most techniques have ↓resolution → difficulty for in vivo quantification of (particularly mixed) lesions.	- Advanced imaging can facilitate TN/PD distinction; however, clinical feasibility is still limited by several remaining issues. - Critical need for further development and greater clinical use of functional imaging biomarkers → conventional imaging is insufficient for radiographic characterization of effects produced by new and combinatorial treatment regimens
Caroline & Rosenthal (2012)[64] **- Systematic Review** **- Assesses efficacy of imaging modalities to distinguish between PP, TN, and PD (HGGs).**	26 clinical studies - 4 main groups of imaging modalities: MRI, PET, SPECT, and combinations thereof.	*MRI-based techniques:* - Conventional Gd-MRI and MRS appear to be more sensitive than specific. - MR perfusion using rCBF appears to be more specific than sensitive. - DWI and DTI appear to have similar accuracy (86.7% and 85.7%, respectively) in detecting PD *PET / SPECT:* - ^{201}Tl-SPECT may be more specific (100% specificity / 84–100% sensitivity range) than FDG or amino acid based PET tracers. - Combined MRI w/ ^{201}Tl-SPECT may have ↑sensitivity than combined MRI w/ ^{18} F-FDG-PET; using combinations of PET tracers may exceed the level of diagnostic accuracy reached by single tracers alone.	- Many included studies had small sample sizes or were not biopsy-controlled - Overall lack of prospective biopsy-controlled studies in the field	- No specific recommendations on preferred imaging techniques given - Advocated need for large, prospective, biopsy-controlled studies.

Table 1 *Continued*

Study/Type	No./Types of Studies Reviewed	Selected Notable Findings	Key Issues Identified	Overall Recommendations
Shah et al, (2013)[40] **- Systematic Review** **- Assesses case reports/ case series/prospective studies for efficacy of imaging modalities to distinguish TN from recurrent glioma.**	17 clinical studies - All selected studies included at least 1 case of histological confirmation.	- SPECT had the highest combined mean specificity (97.8%) out of the reviewed studies. Its mean sensitivity (87.6%) was comparable to that of conventional MRI, the most sensitive modality (88.9%) - MET-PET has ↑mean sensitivity and specificity (84.2% and 82.4%, respectively) than FDG-PET (70.1 and 64.8%, respectively). - CTP combined with a permeability surface air product (PS) yielded 100% sensitivity, 89% specificity in a biopsy-controlled cohort of 38 pat. (Jain et al, 2011)	*Limitations noted in own review:* - No differentiation between TN and PP made in analysis - Predominance of PD cases over TN cases → potential bias in sensitivity/ specificity values *Other identified issues:* - Potential operator dependency/ subjective bias in studies - Clinicians must ensure that technology is available and that neuroradiologists are familiar with it.	- SPECT, in particular Tc-99 SPECT, may be the modality of choice for diagnostic purposes. - CTP is recommended if maximal sensitivity for detection of PD is clinically desired. - MRI alone and ^{18}F-FDG-PET have low specificity and should be avoided.
Verma et al, (2013)[12] **- Comprehensive Review** **- Discusses efficacy and limitations of structural & functional imaging modalities in distinguishing TN from PD.**	Tabular analysis of: - 8 DWI /DTI studies (ADC and FA values) - 10 perfusion studies (MR or CT-based) - 14 MRS studies (MRS ratios) - 16 PET studies - 14 SPECT studies	*DWI/DTI:* Remains largely at exploratory stage, awaits thorough evaluation. - Measurements (esp. ADC values) affected by scanner type, magnetic field strength → difficult to establish standardized parameters and universal threshold values to differentiate TN from PD. - Effects of necrosis, gliosis, fibrous scar tissue, tissue granulation on ADC and FA values not well understood - Mean ADC and FA values easily skewed by mixed lesions. *Perfusion imaging:* Variable Pro/Con profile for each technique. DSC MR imaging potentially most clinically feasible. - DSC MRI: *Pros*- better SNR, shorter scan times, ease of use, better availability. *Cons*- prone to susceptibility artifacts → limited application in pat. w/ hemorrhages, calcifications, surgical clips. - DCE MRI: *Pros*- robust against susceptibility artefacts, ↑spatial resolution that better characterizes mixed lesions. *Cons*- complex/error prone hemodynamic parameter quantification → no FDA-approved standardized software exists. - CTP: *Pros*- technology widely available, no magnetic susceptibility artefacts, parameter quantification linear and less error prone. *Cons*- ↓clinical feasibility than MRI → toxicity (ionizing radiation, iodinated contrast agents), ↓resolution, image acquisition and processing less flexible. *MRS:* Multivoxel MR measuring abnormal spectra beyond the contrast-enhanced area could help detect extent of perilesional tumor infiltration → potential for improved radiation field mapping/ reduction of TN risk. - Frequent tissue necrosis in PD may metabolically mimic TN (↑lipid and ↑lactate levels) - Prone to ↑variability (low SNR, acquisition- and biological variability, inaccurate voxel relocalization during spectrum averaging) → ↓reproducibility of measurements - Limited clinical feasibility → long scan times, high cost, no insurance coverage, lack of universal consensus (↑metabolite ratio variability across studies) *Multimodal imaging:* - In a prospective, biopsy-controlled study, structural MRI when used in conjunction with FET-PET and MRS could boost accuracy of PD detection from 68% to 97% (Floeth et al, 2005)	Majority of studies focus on single imaging modalities only, have small sample sizes, lack biopsy-control Limited clinical utility: - ↓scanner availability - lack of insurance coverage - ↑operation costs - frequent diagnostic need for multiple combined imaging techniques further limits clinical feasibility	- Multiple combined imaging techniques should be used in case of mixed lesions to yield a) better physiological characterization of lesions and b) reduce misinterpretation of lesions. - Results from multimodal diagnostic imaging should be contextualized with info on patient demographics, therapeutic history, and primary tumor type. - Quantitative approaches using morphometric image feature analysis to detect fine-grained differences between TN and PD warrant further investigation.

Table 1 *Continued*

Study/Type	No./Types of Studies Reviewed	Selected Notable Findings	Key Issues Identified	Overall Recommendations
Ryken et al. (2014)[20] -Systematic Review -Focus on which imaging techniques best differentiate PD from TN and PP in patients with previously diagnosed GBM.	57 clinical studies, 46 focused on advanced imaging techniques -8 MRI perfusion studies -5 MRI diffusion studies -13 MRS studies -10 PET studies -10 SPECT studies	See detailed imaging recommendations with corresponding levels of evidence (Class I–III)[a]. *Multimodal imaging:* - Combined use of multiple imaging techniques and multi-parametric analyses are classified as class 3 data (lacking independent validation), but may offer greatly improved diagnostic accuracy - A 55 pat. cohort study (36 pat. w/ biopsy-confirmed diagnosis) showed a 96% diagnostic accuracy of MRS combined with DWI in detecting TN vs PD (Zeng 2007)	- Reviewed studies lack high levels of evidence due to: -poor study design -heterogeneity of pat. population -variability in practices at time of progression- MRS (*Level II*) or SPECT (*Level III*) - Paucity of prospectively collected data with as diagnostic methods for PD vs TN / PP differentiation. - Routine use of PET to identify PD is not recommended (*Level III*)	- MRI (w/ or w/o Gd.) as imaging surveillance method to detect progression of GBM (*Level II* evidence)

Abbreviations: ^{11}C-MET = (11)c-methionine; ^{18}F-FDG-PET = fluorodeoxyglucose; ^{18}F-FDOPA = fluorodopa; ^{18}F-FET = fluoro-ethyl-tyrosine; ^{201}Tl = (201)thallium; ADC = apparent diffusion coefficient; Cho = choline; Cr = creatine; CTP = computed tomography perfusion imaging; DCE = dynamic contrast-enhanced; DSC = dynamic susceptibility contrast; DTI = diffusion tensor imaging; DWI = diffusion weighted imaging; FA = fractional anisotropy; GBM = glioblastoma multiforme; Gd = gadolinium; HGG = high-grade glioma; LGG = low-grade glioma; MRI = magnetic resonance imaging; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate; pat. = patients; PD = progressive disease; PET = positron emission tomography; PP = pseudoprogression; rCBF = regional cerebral blood flow; Rx = radiation; SNR = signal-to-noise ratio; SPECT = single-photon emission computed tomography; Tc-99 = technetium-99; TN = treatment necrosis; w/ = with; w/o = without

[a] Grading of evidence levels in this study was carried out according to "a three-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) Joint Committee on Guidelines criteria."

experience and personal judgment. As the histopathological distinction between TN and PP remains challenging, findings are often summarized under the umbrella term "treatment effect." Moreover, analyzed lesions frequently reveal "mixed results," consisting of necrosis with differing quantities of scattered atypical tumor cells and/or foci of solid tumor (representing PD), thus making re-initiation of anti-neoplastic treatment a judgment call. Occasionally, lesions may contain inflammatory components, such as lymphocytic infiltrates, rather than plain necrosis. While rare atypical cells are found in most TN specimens, radiation-induced cellular atypia in non-neoplastic cells is a known phenomenon that may cause further diagnostic ambiguity.[6]

Establishing treatment effect–specific quantitative and qualitative measures for (i) more accurate histopathological differentiation between distinct types of TN or other treatment-induced phenomena like PP, and (ii) precise determination of the amount of tumor versus treatment-related pathology within the specimen would improve diagnostic accuracy and aid further patient management decisions and prognostication. Such measures may be more conceivable for specimens resected in toto, as tissue samples obtained by stereotactic needle biopsy—depending on the amount of available tissue—carry a higher risk of sampling error and non-diagnostic yield.[70]

Therapeutic Considerations

The clinical course of patients diagnosed with TN is highly variable. Necrotic lesions may develop entirely without symptoms (identified by neuroimaging only), but approximately 42%[34] to 54%[15] of patients will demonstrate progressive cognitive decline, diffuse and/or focal neurological deficits, signs of increased intracranial pressure, and/or seizures[71] (ie, frequently mimicking the clinical picture of PD) (Fig. 1). While clinical symptoms may resolve gradually, some patients will get progressively worse, requiring medical and/or surgical therapeutic intervention to halt further neurological decline or, rarely, to prevent a fatal outcome.[72] The rather ill-defined heterogeneous clinical picture of TN along with aforementioned radiological difficulties pose a management challenge,[1] as therapeutic strategies for TN differ sharply from those for PD.[73]

No SOC treatment protocol for TN presently exists and the pathophysiology of the condition remains poorly understood. Histopathological correlates of TN commonly include thrombosis, hemorrhage, parenchymal necrosis, histiocytic infiltrates, gliosis, fibrinous exudates, and vascular abnormalities.[6] While thought to be driven by a combination of treatment-induced vascular endothelial injury, glial cell injury, hypoxic injury/vascular endothelial growth factor (VEGF) overexpression and (auto)immune-mediated responses,[6,8,9,17] the exact sequence of pathomechanisms and key targetable molecular drivers of TN remain uncertain.

Among numerous therapeutic strategies put forward for TN (see Supplementary Table 1 for a comprehensive

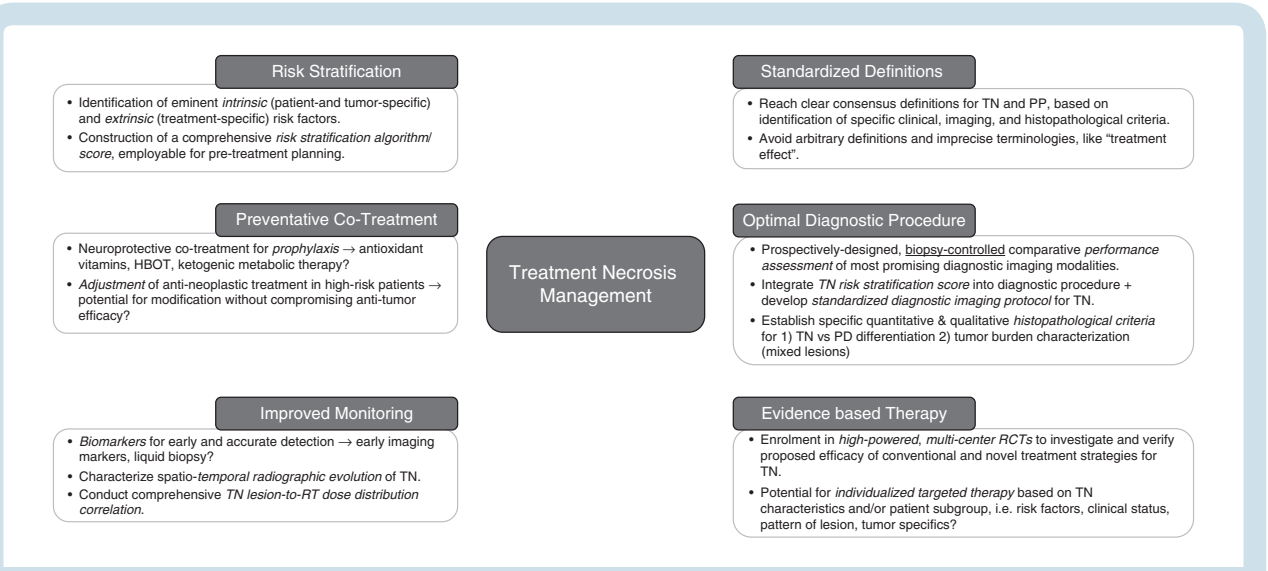

Fig. 4 Schematic illustrating 6 eminent, interdependent research pillars paramount to mapping the field of treatment necrosis management in neuro-oncology. Key research topics and unanswered questions are highlighted.

overview of relevant published studies), no causal therapy is presently available as existing interventions are mostly limited to management of TN-associated symptoms.[5] As such, vasogenic edema and associated mass effect, thought to be caused by radiation-induced blood–brain barrier disruption and inflammatory cytokine release,[9,74] are commonly managed with corticosteroids.[75] More recently, the VEGF-A monoclonal antibody bevacizumab (Avastin) has shown some promise in reversing neurological symptoms and radiographic changes in patients with TN.[27,76–80] However, the long-term therapeutic feasibility of both medications is limited by their side effect profiles[81] as well as treatment costs (in the case of bevacizumab).[79] Single case reports of patients with TN experiencing paradoxical neurological worsening under bevacizumab treatment[82] or developing acquired resistance to the drug[83] have been documented. Anti-coagulant/anti-platelet drugs with vitamin E,[84–86] hyperbaric oxygen therapy (HBOT),[87–89] intramuscular nerve growth factor,[90] and antibiotic applications[91] constitute other experimental strategies, although response rates have been mixed and associated studies were generally of insufficient levels of clinical evidence.[5,10] Minimally invasive techniques, such as laser interstitial thermal therapy (LITT),[92–94] are being increasingly explored to treat TN or PD lesions that are surgically inaccessible[94,95] and/or located in eloquent brain regions,[96] or when open surgical procedures are contraindicated. Evidence from 2 biopsy-controlled retrospective studies[95,97] and 1 multicenter prospective study has suggested clinical and radiographic improvement from LITT with minimal morbidity in patients with previously symptomatic TN lesions.[98] Finally, surgical resection carries an implicit advantage of yielding diagnostic histopathological information that may guide future patient management. While potentially a life-saving intervention in the management of acutely symptomatic, mass-effect producing TN lesions, surgical intervention may bear the risk of procedure-related complications and worse neurological outcome.[72] Delayed timing of surgery (usually after all conservative therapy has failed) may propel surgical risk, whereas more aggressive, early surgical intervention could potentially improve clinical outcome.[72]

Taken together, existing therapeutic options for patients with TN are limited. Most available treatment strategies lack sufficient clinical evidence to draw dependable conclusions on their possible therapeutic efficacy. Bevacizumab appears to have the most evidence to suggest favorable effects on both clinical and radiographic improvement as well as reducing steroid dependency, although the side effect profile and high treatment cost may preclude its long-term therapeutic feasibility.[27,77,79,80] Intra-arterial anti-VEGF therapy might potentially reduce bevacizumab-associated side effects[99,100]; however, its efficacy remains to be shown in glioma patients affected by TN. Intramuscular nerve growth factor treatment has shown some early promise in reversing cognitive deficits and radiographic findings without significant adverse effects in patients with temporal lobe necrosis, warranting further investigation.[90] Finally, the use of LITT to treat surgically inaccessible symptomatic TN lesions bears promise in alleviating neurological symptoms and reducing the need for steroids without the risk of conventional surgical approaches.[95,97,98]

Future Perspectives: Mapping the Field

Improvement in the management of TN faces a number of clinical and systemic challenges (Fig. 1 and Fig. 2).

While an array of advanced diagnostic imaging modalities and therapeutic strategies have been developed (Table 1 and Supplementary Table 1), no diagnostic or therapeutic consensus for TN presently exists. High-powered, prospective, and biopsy-controlled clinical studies may help to improve performance assessment of diagnostic neuroimaging and provide the basis to establish dependable, treatment-effect specific imaging criteria to supplement existing modified RANO criteria.[45] Moreover, sufficient availability of biopsy material would facilitate research to advance histopathological characterization for different types of treatment effects (Fig. 3).

In addition to defining an evidence-based diagnostic and therapeutic SOC, future work should address prevention strategies and improved patient monitoring (Fig. 4). The former will necessitate assessment of putative risk factors for TN and, optimally, the construction of a clinically employable risk stratification tool to identify "high risk patients." Adjustment of cancer therapy regimens and use of potential neuroprotective strategies, such as ketogenic metabolic therapy,[101] high-dose antioxidants,[86] or HBOT,[88] during and after chemo-RT treatment are possible areas of investigation. Here, clinical evaluation should ideally include a non-inferiority design, to ensure that tumor response is not adversely affected. Additional challenges to clinical trial design relate to patient selection criteria, that is, whether stratification of patients with TN based on the underlying condition (malignant glioma, brain metastases, or nasopharyngeal carcinoma) would be reasonable. Finally, greater emphasis on comprehensive evaluation of treatment-related effects across the entire neuro-oncological care trajectory would permit more integrated analysis of collected clinical data.

Conclusion

Progress in this complex field of TN is limited by several clinical and systemic factors. Critical questions pertaining to the true incidence and presentation of TN, risk factors, histopathological correlates, radiographic patterns, and the role of advanced functional imaging modalities remain to be addressed. Deriving conclusive answers from the current body of literature is chiefly precluded by the paucity of biopsy-controlled studies. A greater research focus on treatment-related effects through rigorous collection of clinical data and inclusion of relevant parameters as primary or secondary endpoints in multicenter randomized controlled trials would be of tremendous benefit to improve prevention, diagnosis, treatment response assessment, and therapeutic management of affected patients.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

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