

## MORPHOLOGICAL AND PROGNOSTIC SIGNIFICANCE OF TUMOR NECROSIS IN BREAST CANCER.

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**Abstract.** Tumor necrosis is an important histopathological feature in the assessment of the morphological and biological characteristics of breast cancer. Necrosis may develop as a consequence of rapid tumor growth, inadequate blood supply, and intratumoral hypoxia. Recent studies have demonstrated associations between tumor necrosis and high histological grade, increased proliferative activity, hypoxia-related molecular alterations, and certain aggressive molecular phenotypes. In addition, the extent and spatial distribution of necrosis within the tumor may influence its prognostic significance. This literature review analyzes the mechanisms underlying tumor necrosis in breast cancer, its morphological characteristics, associations with molecular subtypes, and prognostic significance based on current scientific evidence.

**Keywords:** breast cancer, tumor necrosis, hypoxia, HIF-1 $\alpha$ , Ki-67, histological grade, molecular subtype, triple-negative breast cancer, prognosis.

**Background.** Breast cancer is a morphologically and molecularly heterogeneous disease whose clinical course depends not only on histological type, tumor size, and regional lymph node status, but also on the characteristics of the tumor microenvironment and tumor metabolism. When rapid expansion of the tumor mass exceeds the capacity of the existing vascular network to provide adequate oxygen and nutrients, intratumoral hypoxia develops. Severe and prolonged hypoxia may result in irreversible cellular injury and necrosis [1–3]. Therefore, tumor necrosis is increasingly considered not merely a degenerative histological finding but also a potential indicator of tumor biological activity and the state of its microcirculation.

**Objective.** To analyze the mechanisms of tumor necrosis, its morphological characteristics, association with molecular subtypes, and prognostic significance in breast cancer based on current scientific literature.

**Materials and Methods.** This study was conducted as a literature review. Scientific articles, reviews, and clinicopathological studies addressing tumor necrosis, intratumoral hypoxia, HIF-1 $\alpha$  signaling, proliferative activity, histological grade, and molecular subtypes of breast cancer were analyzed. Particular attention was given to recent publications investigating the morphological and prognostic significance of tumor necrosis.

**Literature Review.** Histologically, tumor necrosis is characterized by aggregates of dead and disintegrating tumor cells forming amorphous coagulative material containing nuclear and cytoplasmic debris [1]. In breast carcinoma, the development of necrosis is closely associated with inadequate oxygen delivery to rapidly proliferating tumor tissue. As tumor cells exhibit increased proliferative and metabolic activity, their oxygen demand rises; however, the abnormal vascular network formed through tumor angiogenesis may be unable to meet this requirement. Consequently, hypoxia develops particularly in tumor areas located farther from functional blood vessels and, when sufficiently severe, may lead to necrotic cell death [2,3]. At the same time, hypoxia activates adaptive mechanisms in surviving tumor cells. Hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) is one of the major transcriptional regulators involved in this response and promotes the expression of VEGF and other angiogenic factors, enhances glycolytic metabolism, and facilitates tumor-cell adaptation to hypoxic conditions [2–4].

Tumor necrosis and hypoxia are also closely related to the morphological phenotype of breast carcinoma. Intratumoral oxygen deficiency may affect cellular proliferation, differentiation, growth pattern, fibrosis, angiogenesis, and immune-cell infiltration [2]. Consequently, necrosis is frequently observed in biologically active and high-grade carcinomas. Nevertheless, the presence of necrosis should not automatically be interpreted as having the same adverse prognostic significance in every patient. Chen et al. evaluated 471 patients with invasive

breast cancer and assessed not only the presence of necrosis but also its spatial relationship with tumor cells, collagen fibers, and other tissue components [1]. Using a tumor-necrosis scoring approach, the investigators demonstrated that patients with high-risk necrotic patterns had poorer 5-year disease-free survival than patients without necrosis, whereas the outcome of patients with low-risk necrosis was closer to that of the non-necrotic group [1]. These findings suggest that the prognostic significance of necrosis may depend not only on its presence or extent but also on its spatial heterogeneity within the tumor.

The association between tumor necrosis and molecular subtypes is another important area of research. Luminal A, Luminal B, HER2-positive, and triple-negative breast cancers may exhibit different biological responses to hypoxic stress [2,4]. Triple-negative breast cancer (TNBC), in particular, is considered an aggressive phenotype frequently characterized by high proliferative activity and a hypoxic tumor microenvironment. Activation of HIF-1 $\alpha$  signaling in TNBC may promote glycolysis, angiogenesis, invasion, metastatic progression, cancer stem-cell properties, and mechanisms of immune escape [4]. Molecular studies have also associated tumor necrosis with activation of biological programs related to proliferation, hypoxia, stemness, and epithelial–mesenchymal transition [5]. Therefore, the relatively frequent occurrence of necrosis in TNBC and other aggressive phenotypes may be biologically linked to rapid tumor growth and the development of a hypoxic microenvironment.

Thus, tumor necrosis in breast cancer should be considered not simply as an isolated degenerative feature but as part of the integrated morphological and molecular profile of the tumor. Assessment of the presence and extent of necrosis together with Nottingham histological grade, Ki-67 proliferative index, ER, PR and HER2 status, molecular subtype, regional lymph node involvement, and other prognostic factors may provide a more comprehensive characterization of tumor biology [1–5]. In particular, combined investigation of the spatial heterogeneity of necrosis and hypoxia-related molecular markers may improve prognostic

assessment and contribute to a better understanding of the biological behavior of breast cancer.

**Conclusion.** Tumor necrosis is an important morphological feature of breast cancer associated with intratumoral hypoxia, inadequate blood supply, and increased metabolic and proliferative activity of tumor cells. Although the presence of necrosis may be associated with high histological grade, aggressive molecular phenotypes, and poorer clinical outcomes, its prognostic value may vary according to the extent and spatial characteristics of the necrotic areas [1,2]. Therefore, tumor necrosis should be evaluated in combination with other prognostic parameters, particularly histological grade, Ki-67 proliferative index, hormone receptor status, HER2 status, and molecular subtype. Such an integrated approach may improve the morphological characterization and prognostic assessment of breast cancer.

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