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Review Article

Turgut Anuk[1], Hatice Beseren[2], Ozgecan Hamdemir[2], Ahmet Basak[3]

[1]SBU Erzurum Faculty of Medicine, Department of General Surgery, Erzurum Türkiye
[2]Kafkas University Faculty of Medicine, Department of Pathology, Kars, Türkiye
[3]University of Heatlh Sciences, Erzurum Region Health Research, Turkey

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Corresponding Author: Turgut Anuk, Erzurum Faculty of Medicine, Department of General Surgery, Erzurum Türkiye
Email: turgutanuk@gmail.com

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Changes in receptor levels and mutation profiles after surgery: adaptation and heterogeneity in tumor biology

Abstract

Malignant tumors are dynamic entities that evolve not only histologically but also at the molecular level. Variations in receptor expression (e.g., ER, PR, HER2) and alterations in mutation profiles observed in residual or recurrent tumor tissue after surgical resection highlight both the adaptive capacity of tumor cells and intratumoral heterogeneity. This molecular evolution is largely driven by the emergence of new genetic subclones shaped by clonal selection and microenvironmental pressures. Postoperative changes—including hypoxia, inflammation, and stromal remodeling—further promote immune evasion, epithelial–mesenchymal transition (EMT), and the development of treatment-resistant phenotypes. These processes may lead to receptor status divergence in metastatic or recurrent lesions compared to the primary tumor, necessitating reassessment of therapeutic strategies. For pathologists, repeating immunohistochemical and molecular testing on metastatic or recurrent samples is critical for optimal clinical management. This review evaluates molecular adaptation in tumor biology following surgery, with a focus on receptor conversion, mutational diversity, clonal evolution, microenvironmental interactions, and implications for pathological reporting.

Keywords: Tumor biology, surgery, receptor conversion, mutation profile, heterogeneity, clonal evolution, pathology

INTRODUCTION

Tumor biology is not merely confined to abnormalities in cellular proliferation and differentiation; rather, it is a dynamic and complex, multilayered process. In recent years, numerous studies have demonstrated that malignant neoplasms undergo not only histological but also molecular changes (1,2). Particularly in residual or recurrent tumors after surgical resection, alterations in receptor expression and mutation profiles indicate the tumor cells' capacity for adaptation and their evolutionary trajectory through clonal selection (3).

One of the primary mechanisms underlying these molecular changes is intratumoral heterogeneity, defined as the emergence of genetically diverse subclones from a single clonal origin. Multiregional sequencing studies by Gerlinger et al. have revealed substantial genetic diversity even within primary tumors (4). Surgical intervention can eliminate certain subclones

within this heterogeneity, while allowing others with adaptive capabilities to predominate. In breast cancer, for example, this process may result in receptor conversion involving biomarkers such as estrogen receptor (ER), progesterone receptor (PR), or HER2 (5,6).

These molecular alterations after surgery also carry significant implications for pathological assessment. Discrepancies in receptor levels between primary tumors and metastatic sites necessitate retesting of key markers, directly influencing therapeutic planning (7). Therefore, for pathologists, it is essential to repeat immunohistochemical and molecular analyses on biopsy samples from recurrent or metastatic lesions to guide clinical decisions accurately (8).

Moreover, postoperative changes in the tumor microenvironment, such as hypoxia, stromal remodeling, and immune cell infiltration, can activate new signaling pathways in tumor cells. This, in turn, initiates biological processes such as epithelial–mesenchymal transition (EMT), angiogenesis, and immune evasion, thereby promoting the development of treatment-resistant clones (9,10).

This review examines the molecular alterations observed after surgery in terms of receptor expression, mutation profiles, and changes in the tumor microenvironment. Furthermore, it discusses the implications of these alterations for pathological evaluation, the necessity of repeat biopsies, and their impact on treatment strategies, integrating current literature. In doing so, it aims to provide a holistic understanding of the link between the dynamic nature of tumor biology and its clinical and pathological significance.

Receptor Expression Changes (Receptor Conversion)

One of the most frequently observed molecular changes following surgery in tumors involves alterations in the expression of clinically critical proteins such as hormone receptors (estrogen receptor (ER), progesterone receptor (PR)) and growth factor receptors (most notably HER2). This phenomenon, known as receptor conversion, refers to a shift in receptor positivity between the primary tumor and recurrent or metastatic lesions.

In a large-scale study of breast cancer cases, Lindström et al. reported that ER and PR expression changed in approximately 20–40% of recurrent tumors post-surgery, while HER2 status differed in 10–15% of cases (7,8). Similarly, Dieci et al. emphasized that receptor conversion rates across different breast cancer cohorts significantly influenced clinical treatment management (9,10). These changes are critical for treatment decisions, as the effectiveness of endocrine therapy in hormone receptor-positive tumors largely depends on receptor presence.

Although the exact causes of receptor conversion are not fully understood, postoperative microenvironmental pressure, clonal selection, and epigenetic modifications are considered key contributing factors. Additionally, sampling bias and technical variations may also contribute to these differences (11).

From a pathological standpoint, it is essential to obtain a new biopsy and repeat immunohistochemical testing after surgery to accurately determine the current receptor status. This approach is crucial for optimizing treatment response and preventing unnecessary or inadequate therapies.

Tumor Heterogeneity and Clonal Evolution

One of the core elements of tumor biology, intratumoral heterogeneity, is defined as the presence of cellular subpopulations within the same tumor mass that possess distinct genetic, epigenetic, and phenotypic characteristics. This heterogeneity is associated with clonal diversification driven by selective pressures such as hypoxia, immune responses, and therapeutic interventions during tumor evolution (11). Subpopulations formed by surviving cells following surgery may exhibit genetic and molecular features distinct from those of the dominant clones in the primary tumor. This is especially evident in metastatic or locally recurrent tumors, where receptor conversions and changes in mutation profiles are frequently observed.

A multiregional sequencing study by Gerlinger et al. on renal cell carcinoma demonstrated significant molecular differences between tumor clones (12). This work highlighted the inadequacy of single biopsies in fully capturing the genetic landscape of tumors. Similarly, Marusyk and Polyak emphasized the critical role of clonal evolution in tumor progression and treatment response (13).

Clonal evolution proceeds through a Darwinian selection process. Post-surgical residual cells may adapt to new microenvironmental conditions through diverse genetic pathways. As a result, a previously minor subclone in the primary tumor may become dominant after surgery, giving rise to a more aggressive and treatment-resistant phenotype. This phenomenon helps explain the variability in biological behavior observed in recurrent tumors. It also underscores the necessity of molecular reanalysis of both the primary tumor and recurrent or metastatic lesions, thereby enhancing the diagnostic and therapeutic understanding of clonal evolution in tumor biology.

Selective Pressure of Surgical Intervention and Molecular Adaptation

While surgical resection reduces tumor burden, it also radically alters the tumor microenvironment. Post-resection hypoxia, stromal remodeling, and changes in immune interactions exert strong selective pressures on surviving tumor cells. This selection is not merely the result of physical elimination but reflects molecular-level evolutionary divergence.

Postoperative local hypoxia in the tumor microenvironment

leads to increased expression of angiogenic factors such as VEGF and drives metabolic adaptations in cells. Cells with selective advantages under hypoxic conditions can evolve into more aggressive, invasive, and treatment-resistant phenotypes via transcription factors such as HIF-1α (14). Additionally, postoperative immune activation and immune parameters such as macrophage polarization are crucial determinants of tumor evolution (15).

At the molecular level, changes in gene expression patterns, receptor levels, and even mutational burden may be observed after surgery. Meric-Bernstam et al. reported significant alterations in the expression of critical receptors (e.g., HER2, EGFR) when comparing tumor tissues before and after surgery—findings particularly relevant to targeted therapies (16). These changes not only transform the tumor phenotype but also modify its therapeutic response.

Moreover, minimal residual disease (MRD) left behind after surgery may be reshaped under stromal pressures, giving rise to new clonal arrangements. These emerging clones may carry previously minority mutations and become dominant. Thus, clonal selection plays a central role in reshaping post-surgical tumor biology.

In conclusion, surgical intervention functions not only as a treatment method but also as a selective force that influences the molecular dynamics of the tumor. Consequently, pathological assessments and molecular tests must be repeated in the postoperative period, and treatment strategies should be revised based on this new biological information.

Postoperative Changes in Mutation Profiles

Genetic alterations observed in tumor cells after surgery are critical for understanding adaptation and resistance mechanisms in tumor biology. Residual cell populations may exhibit altered mutation profiles, which is particularly important in recurrent or metastatic tumors, as these changes can influence therapeutic response.

Changes in mutational profiles are linked to clonal evolution, where previously minor or newly emerging clones carrying novel mutations may replace dominant ones. Notably, mutations in key oncogenes and tumor suppressor genes such as TP53, PIK3CA, and ESR1 can appear postoperatively, promoting tumor survival and resistance (10).

Jeselsohn et al. showed an increase in mutational burden in hormone receptor-positive breast cancers following surgery and prior to therapy (11). Similarly, Razavi et al. reported dynamic shifts in mutation profiles after surgery and systemic therapy in advanced breast cancer cases (12).

These mutational changes are not confined to breast cancer but have also been documented in colorectal, lung, and other solid tumors. Repeating mutational analyses post-surgery is essential for designing personalized treatment strategies and for effectively targeting residual disease at the molecular level.

Tumor Microenvironment and Post-Surgical Reprogramming

The tumor microenvironment (TME) comprises tumor cells along with fibroblasts, immune cells, vascular structures, and extracellular matrix components. Surgical intervention induces significant changes in the TME that impact tumor behavior and treatment responsiveness.

Tissue damage after surgery triggers an inflammatory response and the release of various growth factors and cytokines, creating a pro-tumoral environment that enhances residual tumor cell proliferation and invasion (13). Furthermore, phenotypic changes in stromal cells post-surgery—such as the activation of cancer-associated fibroblasts—further promote tumor progression (14).

Modulation of the immune system following surgery also plays a key role in tumor adaptation. An immunosuppressive phase may emerge postoperatively, facilitating immune evasion by tumor cells (15). This reprogramming of the TME may increase the risk of metastasis and resistance to therapy.

Therefore, molecular analyses of both tumor cells and microenvironmental components in postoperative tissues provide a more comprehensive approach for treatment planning.

DISCUSSION

Post-surgical changes in receptor expression and mutation profiles reflect tumor cell adaptation and intratumoral heterogeneity. Surgical intervention not only reduces tumor burden but also imposes selective pressure at both the microenvironmental and molecular levels. This pressure fosters the emergence of new clonal variants and resistance mechanisms (16), initiating a dynamic evolutionary process in tumor biology.

In hormone-sensitive tumors such as breast cancer, receptor conversion after surgery can profoundly alter treatment planning. Lindström et al. reported ER and PR changes in 20–40% of recurrent tumors and HER2 discrepancies in 10–15% (17), directly impacting the effectiveness of targeted therapies. Therefore, repeated biopsies and molecular tests are fundamental components of contemporary clinical practice, even recommended by leading international guidelines like ASCO and ESMO (14-17).

Mutational profile shifts are consistent with clonal evolution, where the emergence of new genetic subpopulations can compromise treatment success. Mutations in genes such as TP53, PIK3CA, and ESR1 increase tumor cell survival and resistance potential (18). Studies by Jeselsohn and Razavi have demonstrated increased mutational burden and the acquisition of new resistance-related mutations following surgery (19).

Reprogramming of the tumor microenvironment after surgery also plays a pivotal role in tumor progression. Postoperative inflammation, stromal activation, and immune modulation enable residual tumor cells to acquire more aggressive and invasive traits (20,21), complicating the management of minimal residual disease and increasing metastatic risk.

The clinical implications of these molecular changes are directly reshaping treatment algorithms. For example, in a breast cancer patient who was initially ER-positive, if a biopsy after recurrence reveals an ER-negative status, it necessitates discontinuing endocrine therapy and switching to chemotherapy. Similarly, the emergence of an ESR1 mutation after surgery is a strong indicator of developing resistance to aromatase inhibitors, and in this situation, a switch to a different endocrine agent like fulvestrant should be considered.

Therefore, close molecular monitoring of tumor biology after surgery is essential for updating treatment strategies.. This dynamic understanding presents new therapeutic opportunities for the future. 'Perioperative' therapies, administered during or immediately after surgery, that modulate the inflammatory response in the microenvironment or prevent the emergence of resistant clones, have the potential to reduce the risk of recurrence. Furthermore, with continuous molecular monitoring through liquid biopsies, 'adaptive therapy' strategies can be developed, where treatment regimens are dynamically adjusted in parallel with the tumor's evolution.

CONCLUSION

Postoperative changes in receptor expression and mutation profiles are key determinants of tumor adaptation and heterogeneity. These molecular alterations directly influence tumor progression, therapeutic response, and prognosis. Thus, updating pathological evaluations and incorporating systematic molecular monitoring after surgery is essential. A deeper understanding of dynamic shifts in the tumor microenvironment also offers new opportunities for developing personalized therapeutic strategies. Integrating molecular surveillance and repeat biopsies into routine clinical practice is vital for optimizing treatment efficacy and improving patient quality of life.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

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REFERENCES

1. Bedard PL, Hansen AR, Ratain MJ, Siu LL. Tumour heterogeneity in the clinic. Nature. 2013;501:355-64.
2. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: a looking glass for cancer? Nat Rev Cancer. 2012;12:323–4.
3. Meric-Bernstam F, Frampton GM, Ferrer-Lozano J, et al. Concordance of genomic alterations between primary and recurrent breast cancer. Mol Cancer Ther. 2014;13:1382–89.
4. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883–92.
5. Lindström LS, Karlsson E, M Wilking U, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and HER2 are unstable throughout tumor progression. J Clin Oncol. 2012;30:2601–8.
6. Dieci MV, E Barbieri, F Piacentini, et al. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a meta-analysis. Oncotarget. 2017;8:62023–33.
7. Amir E, Miller N, Geddie W, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol. 2012;30:587–92.
8. Meng X, Song S, Jiang ZF, et al. Receptor conversion in metastatic breast cancer: a prognosticator of survival. Oncotarget. 2016;7:71887-903.
9. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer. 2009;9:239–52.
10. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metas-tasis. Nat Med. 2013;19:1423–37.
11. Almendro V, Marusyk A, Polyak K. Cellular heterogeneity and molecular evolution in cancer. Annu Rev Pathol. 2013;8:277–302.
12. Marusyk A, Polyak K. Tumor heterogeneity: causes and consequences. Nat Rev Cancer. 2010;10:479–93.
13. Jeselsohn R, Buchwalter G, De Angelis C et al. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol. 2015;12:573-83.
14. Cardoso F, E Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol. 2018;29:1634-57.
15. Razavi P, Chang M, Xu G, et al. The genomic landscape of endocrine-resistant advanced breast can-cers. Cancer Cell. 2018;34:427-38.
16. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;148:399-408.
17. Wafik SED, Taylor B, Neal J et al. Tumor Evolution, Heterogeneity, and Therapy for Our Patients With Advanced Cancer: How Far Have We Come?. Am Soc Clin Oncol Educ Book 2017:37,e8-e15.
18. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860-7.
19. Kalluri R. The biology and function of fibroblasts in cancer. Nat Rev Cancer. 2016;16:582-98.

20. Cheng YQ, Wang SB, Liu JH, et al. Modifying the tumour microenvironment and reverting tumour cells: New strategies for treating malignant tumours. Cell Prolif. 2020;53:e12865.

21. Sosa MS, Bragado P, Aguirre-Ghiso JA. Mechanisms of disseminated cancer cell dormancy: an awakening field. Nat Rev Cancer. 2014;14:611-22.