The prognosis comparison of different molecular subtypes of breast tumors after radiotherapy and the intrinsic reasons for their distinct radiosensitivity

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Abstract: Radiotherapy can increase the cell cycle arrest that promotes apoptosis, reduces the risk of tumor recurrence and has become an irreplaceable component of systematic treatment for patients with breast cancer. Substantial advances in precise radiotherapy unequivocally indicate that the benefits of radiotherapy vary depending on intrinsic subtypes of the disease; luminal A breast cancer has the highest benefit whereas human epidermal growth factor receptor 2 (HER2)-positive and triple negative breast cancer (TNBC) are affected to a lesser extent irrespective of the selection of radiotherapy strategies, such as conventional whole-breast irradiation (CWBI), accelerated partial-breast irradiation (APBI), and hypofractionated whole-breast irradiation (HWBI). The benefit disparity correlates with the differential invasiveness, malignance, and radiosensitivity of the subtypes. A combination of a number of molecular mechanisms leads to the strong radioreistant profile of HER2-positive breast cancer, and sensitization to irradiation can be induced by multiple drugs or compounds in luminal disease and TNBC. In this review, we aimed to summarize the prognostic differences between various subtypes of breast tumors after CWBI, APBI, and HWBI, the potential reasons for drug-enhanced radiosensitivity in luminal breast tumors and TNBC, and the robust radioresistance of HER2-positive cancer.

Keywords: radiotherapy, molecular subtype, breast cancer, molecular mechanism, radiosensitivity

Introduction
Adjuvant radiotherapy is one of the essential components in the treatment of breast cancer and has been recommended in combination with breast-conservation surgery (BCS) for early-stage breast cancer (ESBC) patients and with mastectomy for high-risk patients.1 Compared with total mastectomy and lumpectomy alone, 50 Gy breast irradiation following lumpectomy dramatically lowers the rate of local recurrence (LR) by 7.5% and 6.1%, respectively.2 Moreover, the distant metastasis (DM) rate is decreased in mammary cancer population with radiosensitive characteristics after receiving radiotherapy.3,4 Reduction in overall mortality in breast cancer produced by radiotherapy is essentially identical to systemic chemotherapy.5,6

Multiple radiotherapy strategies are used to treat women at different tumor stages. For the majority of ESBC patients who are qualified for organ preservation, preoperative radiotherapy is a widely adopted standard intervention, whereas postmastectomy radiotherapy is suitable for patients with advanced breast cancer. Nevertheless, not all patients undergoing radiotherapy benefit from it; a large cohort of the patients...
invariably suffer radiation-related adverse effects, including fatigue, telangiectasia, angiosarcoma, skin erythema, and cosmetic damage.\textsuperscript{7–9}

Historically, the implementation of radiotherapy for breast cancer is mainly determined by the following patient-related factors: age, comorbidity, tumor stage, lymphatic vessel invasion, etc. The progress in biological methods in the past two decades has elucidated the heterogeneity of diverse molecular subtypes used to design individualized treatment. According to the expression levels of Ki-67 protein and the status of estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor 2 (HER2), breast cancer can be categorized into four subtypes: luminal A, luminal B, HER2-overexpression, and triple negative breast cancer (TNBC),\textsuperscript{10} which are outlined in Table 1.

Several studies investigated whether the intrinsic molecular subtype of breast cancer can influence the outcome of radiotherapy\textsuperscript{11–13} due to differential prognosis and feedback between chemotherapy and endocrinotherapy.\textsuperscript{14–20} The EORTC 22881-10882 boost vs no boost trial prescribed or did not prescribe a boost radiation dose of 16 Gy to patients with stage I and stage II breast cancer who underwent BCS plus conventional whole-breast irradiation (CWBI) of 50 Gy and found that certain phenotypes of tumors are radioresistant and rarely benefit from extra irradiation dose\textsuperscript{21} suggesting the existence of the dose-benefit gradient of radiotherapy in breast cancer. Therefore, a number of radiotherapy paradigms with low toxicity have been advocated in clinical studies, such as accelerated partial-breast irradiation (APBI) and hypofractionated whole-breast irradiation (HWBI); however, the clinical utility of these methods across four phenotypes of the disease using the same treatment modality is significantly different, which is attributed to inherent radiosensitive or radioresistant properties of the phenotypes to an extent.

The objective of this review was to summarize the prognostic distinctions of various subtypes of breast tumors treated with different radiotherapy methods and to explain the intrinsic reasons for differential radiosensitivity of the subtypes. The molecular mechanisms of cell death induced by ionizing radiation in the tumor and in surrounding normal stem cells are also discussed.

### The comparison of prognosis between four subtypes under various radiotherapy conditions

#### Conventional whole-breast irradiation

For the majority of patients with ESBC or ductal carcinoma in situ (DCIS) in the case of intended breast preservation, standard and widely adopted treatment is CWBI at 50.0 Gy irradiation typically administered at the daily dose of 2.0 Gy via 25 fractions over 5 weeks;\textsuperscript{2,22} this treatment can reduce the risk of LR by 60–70\% and 50–60\% in invasive and noninvasive breast carcinoma, respectively.\textsuperscript{2,23–26} Two independent pioneering randomized trials (The British Columbia Randomized Radiation (BCRR) trial\textsuperscript{27} and The Danish Breast Cancer Group (DBCG) protocol 82b\textsuperscript{26}) demonstrated the benefits of CWBI combined with polychemotherapy in breast cancer. After follow-up of 15 years, the BCRR trial found a reduction in the rate of locoregional recurrence (LRR) and mortality of 33\% and 29\%, respectively, which was approximately similar to the outcomes of DBCG 82b trial that demonstrated a reduction in the LRR rate by 23\% and 9\%, respectively, after 10-years follow-up. These findings have a far-reaching impact on the clinical application of CWBI.

The median time of disease relapse in breast cancer after systemic adjuvant therapy may be 2–4 years or can be significantly prolonged to 5–8 years;\textsuperscript{24,29,30} this delay is linked to tumor biology and molecular subtypes. Compared to luminal breast cancer, TNBC, and HER2-amplified breast carcinomas commonly have strong invasiveness, shortened survival\textsuperscript{31} and a 2–3-fold increase in the tumor relapse rate.\textsuperscript{32,33} Moreover, the risk of DM in TNBC during the initial 2–3 years is higher than that in other subtypes of the disease thus emphasizing unfavorable prognosis.\textsuperscript{34} Multiple studies have corroborated that the prognosis varies depending on the subtype of breast tumor receiving CWBI.\textsuperscript{12,35–37} A significantly lengthened overall survival (OS) is observed in luminal A and TNBC but not in other tumor phenotypes. In breast cancer patients treated with BCS combined with CWBI, the 5 years and 10 years LR risk in TNBC and HER2-positive subtypes (without anti-HER2 targeted therapy) is up to twofold higher than that in luminal A subset and the relapse-free survival in luminal

### Table 1 The classification of four molecular subtypes of breast cancer

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>ER</th>
<th>PR</th>
<th>HER2</th>
<th>Ki-67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>(+)</td>
<td>(+/-)</td>
<td>–</td>
<td>&lt;14%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>(+)</td>
<td>(+/-)</td>
<td>(+/-)</td>
<td>≥14%</td>
</tr>
<tr>
<td>HER2+</td>
<td>–</td>
<td>–</td>
<td>(+)</td>
<td>≥14%</td>
</tr>
<tr>
<td>TNBC</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥14%</td>
</tr>
</tbody>
</table>

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.
B molecular phenotype is lower than that in other intrinsic subtypes; however, the 10 years ipsilateral breast tumor relapse (IBTR) among different subtypes is not significantly different (Table 2). In recent years, alongside with introduction of trastuzumab, the LRR rate of HER2-positive breast cancer has been significantly decreased, however, this high LRR rate remains a major threat in TNBC due to the lack of suitable targeted therapy.

**Accelerated partial-breast irradiation**

Currently, APBI is gradually becoming a surrogate to CWBI due to its discernible advantages including curtailed curative time, superior local control, low toxicity, and favorable cosmetic outcomes. The American Brachytherapy Society has published a consensus statement on APBI treatment for breast cancer by taking the following factors into consideration and enacted appropriate criteria for patient selection: age ≥45 years, tumor size ≤3 cm, negative lymph nodes, no invasion of lymph-vascular space, all invasive histology and DCIS, positive/negative ER status, and no infiltration of surgical margins.

Recently, the correlations of molecular subtypes with the prognosis of breast cancer patients who were treated with APBI have been extensively investigated. In the study of Wadasadawala et al, who evaluated the treatment outcomes of ESBC patients after receiving APBI, it was shown that the 3 years LR and LRR across different molecular subtypes were not significantly different whereas the 3 years DM-free survival, OS, and disease-free survival (DFS) of HER2-positive subtype were significantly lower than those of luminal A and B phenotypes. Moreover, in 2016, Dr. Wilkinson introduced a 5-year follow-up clinical results of APBI treatment in 278 ESBC patients, which indicated no significant difference in the incidence rates of IBTR, DM, DFS, and OS between four phenotypes of breast tumors (Table 2). In contrast,

<table>
<thead>
<tr>
<th>Time</th>
<th>Prognosis</th>
<th>Luminal A (%)</th>
<th>Luminal B (%)</th>
<th>HER2+ (%)</th>
<th>TNBC (%)</th>
<th>p-value</th>
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<tr>
<td>3-year</td>
<td>APBI&lt;sup&gt;42&lt;/sup&gt;</td>
<td>0.0</td>
<td>6.7</td>
<td>12.5</td>
<td>0.0</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>0.0</td>
<td>6.7</td>
<td>12.5</td>
<td>0.0</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>LRR</td>
<td>0.0</td>
<td>97.6</td>
<td>71.6</td>
<td>96.4</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>DMFS</td>
<td>100.0</td>
<td>100.0</td>
<td>82.0</td>
<td>92.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>98.1</td>
<td>93.3</td>
<td>61.0</td>
<td>96.4</td>
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</tr>
<tr>
<td></td>
<td>DFS</td>
<td>100.0</td>
<td>93.3</td>
<td>61.0</td>
<td>96.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5-year</td>
<td>CWBI&lt;sup&gt;32&lt;/sup&gt;</td>
<td>0.8</td>
<td>1.5</td>
<td>8.4</td>
<td>7.1</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td>LR</td>
<td>0.8</td>
<td>1.5</td>
<td>8.4</td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>APBI&lt;sup&gt;45,46&lt;/sup&gt;</td>
<td>0.3</td>
<td>4.6</td>
<td>34.5</td>
<td>11.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>IBTR</td>
<td>3.5</td>
<td>4.1</td>
<td>13.3</td>
<td>11.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>RNR</td>
<td>0.3</td>
<td>4.6</td>
<td>34.5</td>
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<tr>
<td></td>
<td>DM</td>
<td>2.9</td>
<td>1.3</td>
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<td>0.0</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>OS</td>
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<td>92.0</td>
<td>100.0</td>
<td>91.0</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>DFS</td>
<td>95.0</td>
<td>96.0</td>
<td>100.0</td>
<td>95.0</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>HWBI&lt;sup&gt;39&lt;/sup&gt;</td>
<td>2.9</td>
<td>7.9</td>
<td>16.9</td>
<td>4.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10-year</td>
<td>CWBI&lt;sup&gt;32,33&lt;/sup&gt;</td>
<td>12.0</td>
<td>10.0</td>
<td>21.0</td>
<td>14.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>8.0</td>
<td>10.0</td>
<td>21.0</td>
<td>14.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>3.0</td>
<td>8.0</td>
<td>16.0</td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>IBTR</td>
<td>9.0</td>
<td>8.0</td>
<td>19.0</td>
<td>6.0</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>HWBI&lt;sup&gt;56&lt;/sup&gt;</td>
<td>4.5</td>
<td>7.9</td>
<td>16.9</td>
<td>4.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>4.5</td>
<td>7.9</td>
<td>16.9</td>
<td>4.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Table 2** The prognostic comparison of four molecular subtypes of breast cancer under three types of radiotherapy strategies

**Abbreviations:** HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; CWBI, conventional whole-breast irradiation; APBI, accelerated partial-breast irradiation; HWBI, hypofractionated whole-breast irradiation; LR, local recurrence; LRR, locoregional recurrence; DMFS, distant metastasis-free survival; OS, overall survival; DFS, disease-free survival; IBTR, ipsilateral breast tumor relapse; RNR, regional nodal recurrence; DM, distant metastasis.
Pashtan and colleagues evaluated 98 ESBC patients who underwent three-dimensional conformal external beam APBI and discovered partial inconsistencies. The multivariate analysis indicated that TNBC was the only predictor for the inferior outcome of 5 years IBTR with a high risk of 33% compared to that of 2% in other pooled subtypes. There may be some connotative explanations for different conclusion in both trails; for example, the majority of TNBC patients in the latter study receives chemotherapy prior to APBI, thereby delaying the initiation of radiotherapy.

It should be noted that for breast cancer patients >50 years of age undergoing APBI, HER2-enriched subtype has a significantly higher risk of 5 years IBTR and 5 years regiinalnodal recurrence (RNR) than that in all other subtypes, whereas luminal A subtype has the lowest risk of all subtypes. A similar conclusion was reached in some clinical trials following multi-catheter APBI (mAPBI) and single-entry catheter APBI (sAPBI). In the mAPBI trial, HER2-positive status was associated with the shortened DM-free survival, DFS, and OS and the 5 years IBTR of HER2-enriched breast tumors and 5 years RNR of TNBC were significantly higher than those in luminal A disease in the sAPBI trial (Table 2).

### Hypofractionated whole-breast irradiation

Radiobiological models indicate that an alternative regimen, known as HWBI, with a larger daily dose per fraction within a shorter duration may achieve efficacy similar to that of CWBI and has distinct advantages including higher convenience, lower resource expenditure, and decreased LR rate and radiation-related morbidity. In 2002, a randomized trial investigated a 5-year follow-up outcomes with reference to BCS followed by CWBI or HWBI at the 42.5 Gy dose divided into 16 fractions over a period of 22 days in the treatment of breast cancer patients with negative status of axillary lymph nodes. The two cohorts had identical LR rate of 3% and similar cosmetic outcomes reflecting irradiation-associated complications. Considering possible magnification of the radiation-related toxicity at an extended time, women with breast tumors may be inclined to receive HWBI instead of CWBI.

HWBI has become the standard surrogate of CWBI for a large proportion of breast cancer patients; however, it is less effective in high-grade tumors regardless of positive or negative lymph nodes leading to curtailed DFS and deterioration of DM. The highest incidence of LR is observed in HER2-enriched breast cancer patients with lymph node negativity; however, no substantial differences in IBTR rate are detected across four intrinsic subtypes. A study in 752 elderly breast cancer patients (age ≥65 years) who were categorized as having grade 3 primary tumors with positive surgical margins administered a tumor bed boost (n=190). The 5 years DFS of TNBC was significantly lower than that in other subtypes of the tumors (p<0.01) without a significant difference in 5 years LR rate (p=0.83); the univariate and multivariate analysis indicated that HER2-positive breast cancer and TNBC were positively correlated with the unfavorable DFS (p<0.05). A total number of 989 node-negative breast cancer women who underwent HWBI following BCS were finally enrolled in the trial of Dr. Bane and colleagues, demonstrating that the HER2-positive breast tumor was associated with significantly higher 10 years LR than that of Luminal A breast cancer and TNBC (p<0.01) (Table 2). Collectively, the results from these studies demonstrated variable benefit of different phenotypes of breast tumors from CWBI, APBI, and HWBI treatments, which may be attributed to disparate radiosensitivity of the subtypes.

### The reasons for distinct radiosensitivity in individual subtypes

Reparation of DNA double-strand breaks (DDSB) is mainly accomplished through two pathways: non-homologous end joining (NHEJ), the paramount modality of DDSB repair mechanism in terminally differentiated cells that is the dominant pathway in the pre-replicative G1 phase of the cell cycle, and homologous recombination repair pathway (HR) that requires an additional homologous sister chromosome and is the only repair mechanism in the post-replicative S or G2/M phases of the cell cycle. The purpose of radiotherapy is to incite DDSB in the tumor cells to suppress the reparation. Irreversible DNA damage triggers the corresponding cellular mechanisms including cell cycle arrest, apoptosis, and senescence (Figure 1).

In irradiation-induced cell-killing in the tumor, normal stem cells are concomitantly damaged due to their high radiosensitivity. Multiple mechanisms predispose stem cells to radiosensitivity. First, the constitutive expression of PP2A in stem cells antagonizes the DDSB reparation. Second, deacetylation and consequent trimethylation of histone 3
lysine-9 (H3K9) increase the radioresistance in the cells; however, stem cells are prone to acetylation and methylation of H3K9 at different residues. Third, a constitutive level of H3K56 acetylation in the stem cells results in chromatin restraining. Finally, the access of S139 site can be sterically dampened by the close proximity of persistent H2AX-pY142 (Figure 1). These mechanisms collectively reinforce the radiosensitivity, interfere with the repair of DDSB and induce apoptosis in normal stem cells, which may partially explain the irreversible damage to X-ray radiation to the tissues adjacent to the tumor.

The MAP3K4 gene was shown to be a potential target to regulate radiosensitivity,[63] and molecular oxygen is considered as a highly efficient radiosensitizer[64] for breast tumors. The oxygen-dependent radiosensitivity is sharply increased when the partial pressure of oxygen (pO$_2$) elevates from 0 to 10 mmHg and attains its half-maximum value when pO$_2$=3 mmHg;[65] moreover, radiosensitivity

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**Figure 1** The mechanisms of ionizing radiation sensitizing and resistant effects in various subtypes of breast cancer and irradiation-induced apoptosis. The arrows with identical color on different subtypes or cells indicate consecutively acting pathways. **Abbreviations:** VPA, valproic acid; EMT, epithelial-mesenchymal transition; HIS, histamine and its receptor 1 agonist; Piper L, Piper longumine; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; EGFR, epidermal growth factor receptor; EGFRph, phosphorylated EGFR; H3ac/me, acetylated and methylated histone 3; H3K56ac, acetylated H3K56; HR, homologous recombinational repair pathway; NHEJ, non-homologous end joining pathway.
slowly increases once the pO₂ rises above 30 mmHg and up to 100% pure oxygen.\textsuperscript{64,66} One possible explanation of this fact is that a selective accumulation of TAT-ODD-p53 occurs in hypoxic environment inhibiting mitophagy that plays a key role in maintaining hypoxia-induced radioresistance thereby significantly enhancing the radiosensitivity of tumor cells (Figure 1).\textsuperscript{67}

**Luminal breast cancer**

The intrinsic mechanisms of radiosensitivity in luminal breast cancer are well recognized and well documented. A significantly elevated radiosensitivity and a series of favorable anticancer outcomes with slight side effects have been attained by treatment targeted against tumor-related epidermal growth factor receptor (EGFR) in preclinical and clinical studies.\textsuperscript{68,69} The cytotoxic effect of irradiation is increased when the EGFR activity and its downstream signals, such as PI3K-AKT and RAS-MAPK pathways, are downregulated; these pathways can induce cell cycle arrest and apoptosis, suppress cell proliferation and tumor angiogenesis, and reduce the DM incidence.\textsuperscript{70,71}

Luminal subtype of breast cancer can be effectively radiosensitized by treatment with nimotuzumab,\textsuperscript{72} a humanized monoclonal IgG1 antibody, which can block the function of DNA-PKcs and the binding of EGF, TGF-α, and other ligands to EGFR.\textsuperscript{73} This benefit may be attributed to the decreased level of phosphorylated EGFR, induction of cell apoptosis and generation of γ-H2AX, a vital indicator of radiation-induced DSB (Figure 1).\textsuperscript{72,74,75}

Exogenous miR195 can downregulate BCL-2\textsuperscript{76} and ubiquitin-conjugating enzyme E2D3 curtails the accumulation of human telomerase reverse transcriptase and cyclin D1;\textsuperscript{77} the upregulation of expression of these proteins significantly improves the radiosensitivity in luminal breast cancer (Figure 1). In tumor cells, histone deacetylase inhibitors (HDACis) inhibit the repair of DSB via downregulation of the activities of DNA repair proteins, for instance, Rad51, Ku80, and BRCA1.\textsuperscript{78,79} Based on this theory, Jiang et al, treated patients with luminal advanced breast cancer, who did not benefit from endocrine therapy, with a combination of chidamide, an oral subtype-selective HDACis with multiple functions related to repression of tumor growth and modulation of microenvironment by epigenetic reprogramming, with exemestane and found that the median PFS was significantly prolonged in comparison with that in a cohort treated with placebo plus exemestane (7.4 months vs 3.8 months, respectively; p=0.03).\textsuperscript{80} Moreover, valproic acid, which is one of the typical HDACis, at a safe dose of 0.5 mM, can substantially elevate radiosensitivity in the luminal tumor cells by interrupting the molecular mechanism of BRCA1-Rad51-mediated HR and Ku80-mediated NHEJ pathways (Figure 1).\textsuperscript{81}

The thioredoxin (Trx) system is the core enzyme family that controls the redox regulation in the cells and is associated with the irradiation effects in the cancer cells.\textsuperscript{82} Metformin can suppress the Trx expression via the AMPK-FOXO3 pathway that increases the level of intracellular reactive oxygen species (ROS) in the primary humanity aortic endothelial cells to influence redox regulation; metformin can radiosensitize the luminal cancer cells by activating AMPK and suppressing mTOR.\textsuperscript{83} Moreover, metformin can significantly prolong the breast cancer-specific survival in diabetic women with luminal breast cancer;\textsuperscript{84} however, metformin is ineffective in TNBC patients\textsuperscript{85} apparently due to differential metformin-induced radiosensitivity; the effects of the drug are substantial in luminal tumors and are small in TNBC. Several poorly understood reasons may explain unique metformin-induced radiosensitivity; one of the explanations is that changes in ROS levels and attenuation of Trx expression take place in luminal tumors, but these factors remain unchanged in TNBC (Figure 1).\textsuperscript{86}

**TNBC**

Histamine participates in the regulation of growth and differentiation of mammary cells during development, pregnancy, and lactation of females and regulates the proliferation of malignant cells.\textsuperscript{87,88} In luminal breast cancer cells, histamine and histamine H4 receptor (H4R) agonist-based magnification of radiosensitivity is attained by induction of the DSB proteins, such as 8-OHdG, γH2AX, and p53; in TNBC cells, histamine and an H1R agonist also induce the formation of the DSB proteins, including 8-OHdG and γH2AX but excluding p53, elevate ROS levels and upregulate the LCN-2 expression to sensitize the cells to the X-ray effects.\textsuperscript{89} An ex vivo study demonstrated that radiosensitivity was amplified in TNBC by *Piper longumine*, which upregulated the expression of apoptosis-related proteins, BCL2 and BAX, and increases the levels of intracellular ROS (Figure 1).\textsuperscript{90}

Chemokine receptor 4 (CXCR4) promotes trafficking and invasiveness of non-small cell lung cancer cells after ionizing radiation and knockdown of CXCR4 can ameliorate the efficacy of radiotherapy.\textsuperscript{91} A number of in vivo
and in vitro studies demonstrated that combination of AMD3100, a small-molecule CXCR4 inhibitor, with radiotherapy increases radiosensitivity in prostate cancer, glioma, ovarian carcinoma, and TNBC. In TNBC cells, the ADM3100-induced radiosensitivity is elevated due to the accumulation of BAX and caspase-3 and downregulation of BCL-2, thereby arresting the cell cycle in the G2/M phase and eliciting apoptosis (Figure 1).

**HER2 positive breast cancer**

Ionizing radiation can directly activate the EGFR family in tumor cells and reduplicative irradiation at 2 Gy contributes to upregulation of EGFR expression in HER2-enriched breast cancer. These phenomena indicate that HER2-positive status has a potential biological function impacting the radiation response. However, in a retrospective trial conducted on women with lymph node-negative, HER2-positive breast cancer who received BCS and CWBI, the authors represented that the 3 years LRR rate was 1% for the trastuzumab cohort and 9% for the no-trastuzumab cohort, suggesting that the characteristic of HER2-positive breast tumor resisting to irradiation may have little impact on the prognosis of lymph node-negative patients. The molecular mechanisms of the reason for robust radioresistance of HER2-positive breast tumors have been successfully investigated. The transactivation of the NF-κB-mediated HER2 promoter induces HER2 overexpression which is responsible for radioresistance. Furthermore, increased radioresistance is associated with breast cancer stem cells and may be induced by epithelial-to-mesenchymal transition through a key molecular substance named as β-catenin that can be detected in invasive and metastatic HER2-positive tumors. Importantly, in vivo studies have confirmed that substantial clinical benefits can be achieved by inhibiting the Fak-mediated pathway that plays a crucial role in upregulation of the radioresistance of HER2-enriched breast cancer (Figure 1).

**Conclusion**

Radiotherapy significantly ameliorates the prognosis and decreases the incidence rate of life loss in breast cancer patients and has been an indispensable element in the systematic treatment of the disease. Regardless of the use of radiotherapy, luminal A breast cancer has the most favorable clinical outcomes after ionizing irradiation compared to that in HER2-positive cancer and TNBC. Differences in outcomes between these subtypes of the disease are mainly determined by differential radioresistance, aggressiveness, and malignance of the subtypes. X-rays eliminate tumor cells through increased cell cycle arrest, which concomitantly induces an unavoidable severe side effect in normal stem cells in the adjacent tissues. The intensification of radioresistance in HER2-positive breast cancer is ascribed to multiple molecular mechanisms; in contrast, several drugs or compounds sensitize the cells to radiation and increase irradiation efficacy in luminal cancer and TNBC via specific pathways.

**Highlights**

1. Irrespective of the selection of radiotherapy paradigm, luminal A breast cancer has an overall favorable prognosis relative to HER2-positive and TNBC subtypes partially due to individual radiosensitivity of these subtypes.
2. Ionizing irradiation induces ablation of the tumor mainly through increasing the cell cycle arrest to promote apoptosis and senescence; however, ionizing radiation induces serious adverse effects in the normal stem cells in the adjacent tissues.
3. HER2-positive breast cancer has high radioresistance that is correlated to the transactivation of the NF-κB-mediated HER2 promoter inducing HER2 overexpression, β-catenin expression during EMT and the Fak-mediated pathway.
4. Medications or compounds reinforce radiosensitivity in luminal breast cancer and TNBC largely due to an increase in the ROS level and modulation of DNA double-strand break- and/or apoptosis-related proteins, such as 8-OHdG, γH2AX, and p53.

**Abbreviation list**

BCS, breast-conservation surgery; ESBC, early-stage breast cancer; LR, local recurrence; DM, distant metastasis; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; CWBI, conventional whole-breast irradiation; APBI, accelerated partial-breast irradiation; HWBI, hypofractionated whole-breast irradiation; DCIS, ductal carcinoma in situ; LRR, locoregional recurrence; IBTR, ipsilateral breast tumor relapse; DFS, disease-free survival; OS, overall survival; DDSB, DNA double-strand breakage; NHEJ, non-homologous end joining; HR, homologous recombination repair pathway;
H3K9, histone 3 lysine-9; pO₂, partial pressure of oxygen; EGFR, epidermal growth factor receptor; HDACis, histone deacetylase inhibitors; Trx, thioredoxin; ROS, reactive oxygen species; H4R, histamine 4 receptor; CXC R4, chemokine receptor 4.

**Ethics statement**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Disclosure**

The authors report no conflicts of interest in this work.

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