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REVIEW OPEN ACCESS

# Investigation of the Molecular Mechanisms of Paraoxonase-2 Mediated Radiotherapy and Chemotherapy Resistance in Oral Squamous Cell Carcinoma

Mehta Vedant Kamal[1] | Krishnananda Prabhu[2] | Krishna Sharan[3] | Ananth Pai[4] | Sanjiban Chakrabarty[5] | Rama Rao Damerla[6] | Preethi S. Shetty[1] | Vijetha Shenoy Belle[2] | Mahadev Rao[7] | Naveena A. N. Kumar[1]

[1]Department of Surgical Oncology, Manipal Comprehensive Cancer Care Center, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India | [2]Department of Biochemistry, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India | [3]Department of Radiotherapy and Oncology, KS Hegde Medical Academy, Nitte (Deemed to Be University), Mangaluru, Karnataka, India | [4]Department of Medical Oncology, Manipal Comprehensive Cancer Care Center, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India | [5]Department of Public Health and Genomics, Manipal School of Life Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India | [6]Department of Medical Genetics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India | [7]Department of Pharmacy Practice, Center for Translational Research, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India

**Correspondence:** Naveena A. N. Kumar (naveenkumar.an@manipal.edu)

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## ABSTRACT

Oral squamous cell carcinoma (OSCC) is a common form of cancer, with 390,000 new cases estimated for 2022. OSCC has a poor prognosis, largely due to a high recurrence rate and resistance to therapy. Cancer cells develop resistance to standard therapy owing to various factors, such as genetic predispositions, alterations in the apoptotic pathway coupled with DNA repair pathways, drug efflux, and drug detoxification. This review is aimed at exploring the crucial role of paraoxonase 2 (PON2) in conferring resistance to chemotherapy and radiotherapy in OSCC cells. PON2, an antioxidant enzyme, protects cancer cells from the oxidative stress caused by these treatments. By influencing apoptotic pathways and DNA repair mechanisms, PON2 can reduce the effectiveness of therapy. This review is an attempt to explore the complex molecular mechanisms modulated by PON2, such as the mitigation of oxidative stress, enhancement of DNA repair, apoptosis regulation, drug efflux modulation, and drug detoxification, which decrease treatment efficacy.

## 1 | Introduction

Oral cancer ranks as the 16th most prevalent malignancy worldwide and is expected to result in an estimated 389,485 new cases in 2022, accounting for nearly 2% of all human cancers during this period. Moreover, oral cancer is associated with a substantial mortality rate, with approximately 188,230 new fatalities projected to occur due to this disease, corresponding to 1.9% of all cancer-related deaths [1]. Oral squamous cell carcinoma (OSCC) originates from squamous

**Abbreviations:** ABC, ATP-binding cassette; ATM/ATR, ataxia-telangiectasia-mutated/ataxia-telangiectasia-mutated and Rad3-related; Bcl-2, B-cell lymphoma 2; $Ca^{2+}$, calcium ions; CSCs, cancer stem cells; DNA, deoxyribonucleic acid; DSBs, double-strand breaks; EGFR, epidermal growth factor receptor; HIF-1α, hypoxia-inducible factor 1 alpha; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; NER, nucleotide excision repair; NF-κB, nuclear factor kappa B; OSCC, oral squamous cell carcinoma; PI3K-AKT, phosphoinositide 3-kinase-Akt; PON2, paraoxonase 2; ROS, reactive oxygen species; RT, radiotherapy; SSBs, single-strand breaks; UPR, unfolded protein response; Wnt, wingless/Int-1.

cells that line the oral cavity, including the lips, tongue, and floor of the mouth [2]. It is the most prevalent form of oral cancer, accounting for 90% of all oral malignancies [3]. OSCC is characterized by a relatively high mortality rate, especially in locally advanced cases with a five-year survival rate ranging between 50% and 60% [4]. Despite advancements in treatment modalities, the survival rate has remained statistically stagnant, with high recurrence rates and only modest improvements observed in recent decades. Surgery is often the first line of treatment, especially for localized tumors, aiming to excise the tumor with a healthy tissue margin [5]. It may also involve reconstruction techniques to restore functionality and appearance [6]. Radiotherapy (RT) serves as an adjuvant treatment or as an adjunct to surgery and can be employed postoperatively to decrease the chances of local recurrence in locally advanced cases [7]. Chemotherapy is typically administered in conjunction with RT for advanced-stage or as a palliative modality in metastatic OSCC [8]. Targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors and immunotherapy are employed, particularly in cases where conventional chemotherapy alone is not viable, focusing on specific target molecules to inhibit tumor growth and metastasis [9]. Mutations in drug targets, upregulation of deoxyribonucleic Acid (DNA) repair pathways, drug metabolism, and detoxification are well-known factors that can contribute to treatment resistance in patients with OSCC [10]. Recent studies have emphasized the role of cancer-specific antioxidant enzymes such as paraoxonase 2 (PON2) in inducing treatment resistance, leading to poor patient prognosis [11, 12].

The PON2 is one of the three isoforms of the paraoxonase gene family, comprising PON1, PON2, and PON3 [13]. These enzymes are recognized for their antioxidant properties and their ability to hydrolyse various substrates, such as organophosphates, lactones, and aromatic carboxylic acid esters [14]. It exhibits antioxidant properties by mitigating oxidative stress within cells and protecting intracellular molecules from oxidative DNA damage [13, 14]. The PON2 neutralizes reactive oxygen species (ROS), prevents lipid peroxidation, and thus protects cells from oxidative stress [15]. Furthermore, PON2 has been found to maintain mitochondrial integrity and function by precluding oxidative stress-induced apoptosis [16]. Previous studies have reported elevated levels of PON2 in numerous tissues, including the liver, heart, brain, and lungs [17]. Earlier studies have demonstrated that PON2 translocates to the mitochondria and endoplasmic reticulum, where it plays an important role in shielding cells from oxidative stress-induced damage [18]. Numerous studies have elucidated the role of PON2 in suboptimal treatment outcomes and patient survival in various malignancies, including melanoma, pancreatic cancer, stomach cancer, and breast cancer [19]. Elevated PON2 levels are associated with invasive disease and a poor prognosis in certain malignancies [20]. PON2 aids in defending cancer cells from oxidative damage by reducing ROS levels, which increases their ability to overcome the cytotoxic damage induced by various therapeutic agents [21]. Various studies have deciphered the anti-apoptotic function of PON2, suggesting that high PON2 expression can provide a survival edge over various cytotoxic agents that aim to upregulate various apoptotic pathways [11, 22]. PON2 is located on chromosome 7, and this location is shared by other members of the paraoxonase gene family, PON1 and PON3 which are also situated in close proximity to the same chromosome [11]. The anti-apoptotic qualities of PON2 can aid tumor cells in avoiding programmed cell death, which promotes tumor growth and decreases their sensitivity to treatment [22, 23]. The present review examines the diverse mechanisms governed by PON2 that play a significant role in inducing resistance to radiotherapy and chemotherapy in patients with OSCC.

## 2 | Methodology

This review article employed a systematic literature search utilizing PubMed, Google Scholar, and Scopus databases. Keywords such as "PON2," "oral squamous cell carcinoma," "radiotherapy resistance," and "chemotherapy resistance" were employed to identify relevant studies. Inclusion criteria encompassed original research articles, review articles, and meta-analyses published in English. Exclusion criteria comprised case reports, letters to the editor, and studies not directly related to the topic. The identified studies were critically appraised for their methodological quality, relevance, and contribution to the understanding of PON2's role in OSCC. Data obtained focused on key aspects of treatment modalities, PON2 expression levels, and clinical outcomes. Using the extracted data were subsequently analyzed to elucidate potential mechanisms underlying PON2-mediated resistance.

## 3 | Role of PON2 in Radiotherapy Resistance

### 3.1 | Overview of Radiotherapy in OSCC

Radiotherapy is a crucial intervention for the treatment of OSCC because of its ability to induce DNA damage that leads to the destruction of cancer cells [24]. This therapy targets tumors by employing ionizing radiation, including protons, neutrons, or high-energy photons, such as X-rays and gamma rays [25]. Ionizing radiation causes molecules to ionize and form free radicals within cells. These radicals damage DNA, causing single-strand breaks (SSBs) and double-strand breaks (DSBs). The DSBs are particularly hazardous because of the complexity involved in their repair [26]. Cells tend to halt their cell cycle to amend these breaks. If the repair of DSBs is unsuccessful, cells may undergo apoptosis or programmed cell death. In cases of severe damage, necrosis can be observed, which can lead to inflammation [27].

Although RT is an effective treatment for OSCC, several challenges and resistance mechanisms often hinder its success. One major issue is tumor hypoxia or low oxygen levels, which diminish the effectiveness of radiation because oxygen enhances DNA damage [28]. Cancer cells often overexpress DNA repair mechanisms, allowing them to survive the radiation-induced damage [26, 29]. Variations in DNA repair capacity, cell cycle states, and the microenvironment contribute to differing resistance levels among OSCC tumor cells [7, 30]. These tumors are heterogeneous and consist of cells with diverse genetic and phenotypic characteristics. Cancer stem cells (CSCs) are typically more resistant to RT owing to their ability to self-renew and differentiate [31]. If not effectively targeted, CSCs can lead to tumor recurrence [32]. Additionally, radiation can alter the

genetic and epigenetic properties of surviving cells, thereby increasing the risk of further cancer development, metastasis, and resistance to treatment [33]. Some tumors have also developed defense mechanisms against the immune system, enhancing their resistance to RT [30]. Moreover, radiation treatment effectiveness and side effects are influenced by individual patient characteristics, including comorbidities, overall health, and genetic predispositions.

### 3.2 | Molecular Mechanisms of PON2-Mediated Radiotherapy Resistance

Tumor cells exhibit a remarkable ability to adapt to radiation-induced stress through several biological mechanisms, including alterations in gene expression, metabolic reprogramming, and modifications in signaling pathways [34]. PON2 protein has been suggested to be a key player in the adaptive response in enhancing radiotherapy resistance [35]. The role of PON2 in inducing radiotherapy resistance is a significant area of investigation in cancer research, focusing on the mechanisms by which tumor cells evade apoptosis and survive therapeutic interventions.

PON2, located in the nuclear envelope, endoplasmic reticulum, and mitochondria, not only performs antioxidant functions but also exerts anti-apoptotic effects on tumor cells [36]. The endoplasmic reticulum stress caused by unfolded proteins triggers the unfolded protein response (UPR), which affects cell survival or death. This stress can lead to the production of ROS and the release of calcium (Ca2+), disrupting mitochondrial function and exacerbating apoptosis [37]. Overexpression of PON2 alleviates endoplasmic reticulum stress-induced apoptosis and regulates Ca2+ homeostasis [38, 39]. Additionally, PON2 reduces mitochondrial ROS levels and inhibits pro-apoptotic signals [23, 39]. PON2 influences the wingless/Int-1 (Wnt) and beta-catenin (Wnt/β-catenin) signaling pathway, which also plays a role in radiotherapy resistance in cancer cells by controlling cell proliferation, differentiation, and survival [40]. Activation of this pathway stabilizes β-catenin in the nucleus, leading to increased gene expression that promotes cell survival and repair and consequently enhances resistance to radiation-induced DNA damage and oxidative stress [41]. Furthermore, this pathway can also affect the tumor microenvironment, which in turn reduces the efficacy of radiation treatment.

As discussed previously, PON2 significantly enhances DNA repair, scavenges ROS, and regulates the cell cycle, thereby contributing to radiation resistance in cancer cells [13, 23, 42]. It stimulates the ability of cells to amend damaged DNA and increases their resistance to radiation [43]. When exposed to ionizing radiation, PON2 assists in preserving genomic integrity by controlling oxidative stress and cellular metabolism, thereby preventing extensive DNA damage [35, 40]. This increase in DNA repair capacity is closely related to the activation of critical proteins and pathways, particularly the ataxia-telangiectasia-mutated/ataxia-telangiectasia-mutated and Rad3-related (ATM/ATR) pathway [44–46]. The ATM/ATR proteins are essential for detecting and repairing radiation-induced DSBs in DNA [47]. PON2 may stabilize or upregulate the expression of these proteins, facilitating more effective repair of DSBs and SSBs, thereby enhancing cell survival following radiation therapy [11].

PON2 overexpression has been linked to increased radiotherapy resistance, which is partially mediated through the activation of the Phosphoinositide 3-Kinase-Akt (PI3K-AKT) signaling pathway [11, 45]. This pathway is vital for DNA damage repair, cell survival, and inhibition of apoptosis. By enhancing the PI3K-AKT pathway, PON2 facilitates the repair of radiation-induced DNA damage and promotes cell survival [46]. In addition to its impact on the PI3K-AKT pathway, PON2 modulates the nuclear factor kappa B (NF-Kb) signaling cascade, which is a central regulator of inflammatory responses and cell survival [11, 48]. The activation of NF-κB by PON2 leads to the upregulation of anti-apoptotic genes, thereby supporting the survival of cancer cells subjected to RT [11, 49, 50]. Furthermore, PON2 interacts with the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway, which is critical for the cellular stress response [11]. By enhancing MAPK/ERK activity, PON2 contributes to the activation of transcription factors such as hypoxia-inducible factor 1 alpha (HIF-1α), which regulates genes involved in angiogenesis, metabolism, and cellular survival [46]. These pathways are crucial for cellular adaptation to stress induced by radiotherapy, which enhances the ability of tumor cells to survive and thrive (Figure 1). Recent studies have emphasized the role of PON2 in modulating these signaling cascades, significantly influencing radiotherapy resistance.

## 4 | Role of PON2 in Chemotherapy Resistance

### 4.1 | Overview of Chemotherapy in OSCC

Chemotherapy is a treatment option for OSCC, especially when the disease is at an advanced stage or when there are few surgical alternatives available [51]. It works best in combination with radiation therapy (chemoradiation) to enhance therapeutic effectiveness and achieve favorable oncological outcomes [52]. Frequently used chemotherapeutic drugs for OSCC include cisplatin, taxanes, and 5-fluorouracil. Cisplatin creates DNA cross-links that stop transcription and replication, leading to apoptosis [53]. However, enhanced drug efflux, higher DNA repair capacity, and inactivation by thiol-containing compounds (such as glutathione) can lead to the development of resistance in cancer cells [52–55]. Taxanes, such as Paclitaxel and Docetaxel, stabilize microtubules and prevent their disassembly, resulting in apoptosis and disruption of mitosis [56]. Chemotherapy targets mitotically active cells; however, its effectiveness is often reduced because cancer cells develop multiple drug-resistance mechanisms [57]. Drug efflux, in which cancer cells overexpress ATP-binding cassette (ABC) transporters including P-glycoprotein, is the most explored resistance mechanism in various malignancies [58]. This process pumps chemotherapeutic agents out of the cells and lowers intracellular drug concentration and efficacy [59]. Chemotherapy-induced DNA damage does not act as a barrier to the survival and proliferation of cancer cells because of its enhanced DNA repair capabilities [60]. Upregulation of the nucleotide excision repair (NER) pathway confers resistance to traditional platinum-based chemotherapeutic compounds such as cisplatin [61]. Cancer cells can elude chemotherapy-induced

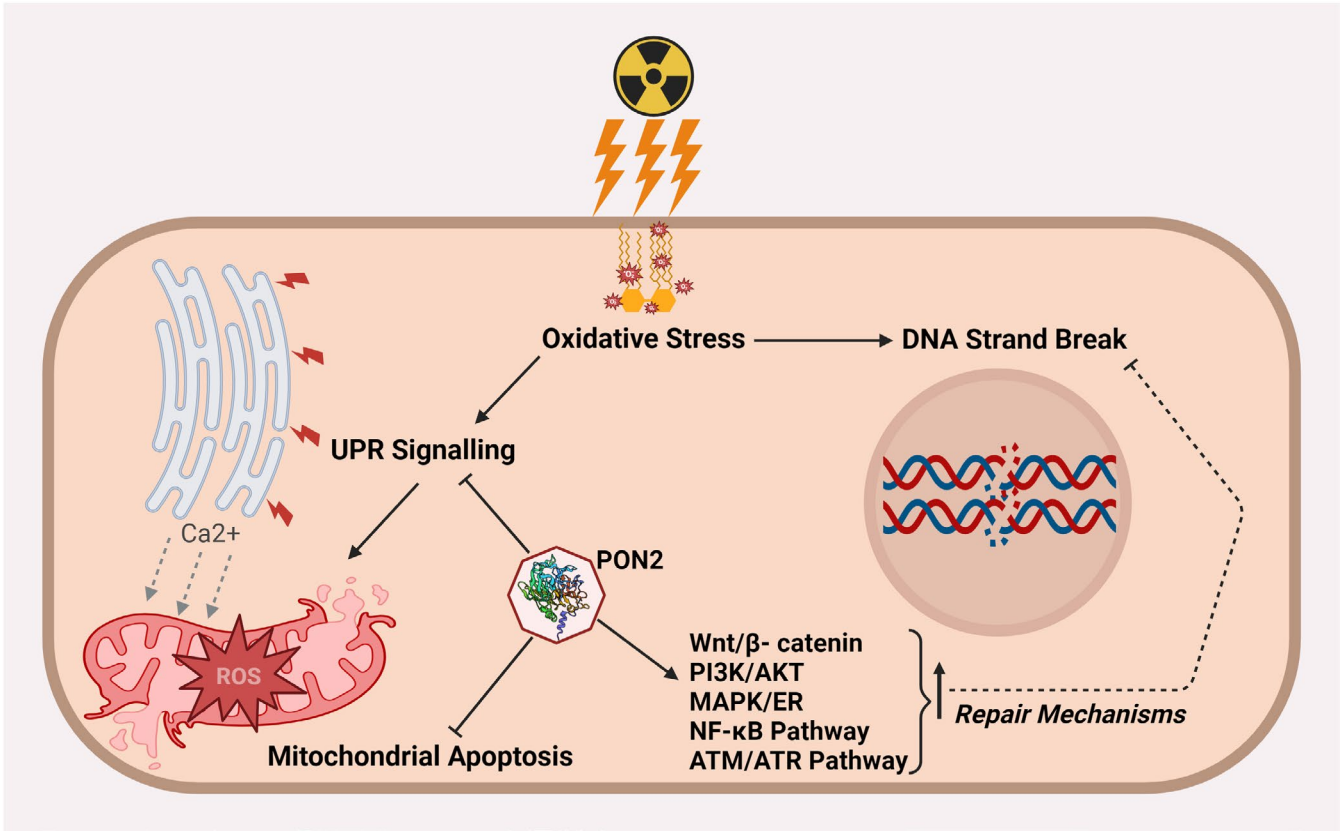


**FIGURE 1** | PON2 augments radiotherapy resistance in tumor cells by mitigating endoplasmic reticulum (ER) stress, reducing mitochondrial reactive oxygen species (ROS), and modulating significant signaling pathways such as Wnt/β-catenin, ATM/ATR, PI3K-AKT, NF-κB, and MAPK/ERK. These mechanisms enable DNA repair, hinder apoptosis, and promote cell survival, which in turn contribute to treatment resistance.

programmed cell death through dysregulation of apoptotic signaling pathways, which include mutations in the p53 tumor suppressor gene or overexpression of anti-apoptotic proteins [62]. Additionally, by upregulating antioxidant enzymes such as glutathione, cancer cells maintain a more reducing microenvironment to counter the oxidative damage caused by chemotherapy [55]. To develop targeted therapeutics to eliminate chemoresistance in OSCC cells, it is essential to comprehend PON2's role in these resistance mechanisms.

### 4.2 | Molecular Mechanisms of PON2-Mediated Chemotherapy Resistance

Recent studies have highlighted the essential function of PON2 in regulating chemotherapy resistance in cancer cells through its antioxidant properties [42, 63, 64]. The PON2 contributes to resistance mechanisms by reducing oxidative stress and preserving cellular integrity [65]. The PON2 protein has been found to be localized in the endoplasmic reticulum, mitochondria, and nuclear envelope; whereby scavenging ROS, PON2 maintains redox equilibrium, prevents lipid peroxidation, and protects membrane lipids from radical-induced damage [66, 67]. This antioxidant defense not only enhances cell survival in adverse environments but also impedes the effectiveness of chemotherapeutic agents [68]. The role of PON2 in the maintenance of glutathione levels, a critical intracellular antioxidant, further reduces oxidative stress and aids in the detoxification of chemotherapeutic drugs [13]. Consequently, decreased oxidative stress and damage enable cancer cells to survive and metastasize, thereby diminishing the efficacy of various cytotoxic agents [69].

Chemotherapeutic drugs such as cisplatin primarily induce DNA damage through ROS production [70]. Some studies have suggested that PON2 may play an indirect role in mitigating the DNA damage caused by these drugs [71]. DNA damage activates checkpoints that inhibit cell division and can lead to apoptosis or cellular senescence [72]. However, PON2's antioxidant properties may limit the effectiveness of these checkpoints, enabling repair of DNA damage and evasion of cell death [73]. Moreover, PON2's modulation of oxidative stress affects several signaling pathways related to cell death and proliferation, influences drug resistance, and reduces treatment efficacy [11]. This protective action is crucial for cancer cells because it inhibits various mechanisms of cell death.

In vitro studies have shown that PON2 plays a crucial role in modulating molecules that control apoptotic pathways, including caspases and proteins of the B-Cell Lymphoma 2 (Bcl-2) family [36, 37, 74]. The Bcl-2 family of proteins, which includes pro- and anti-apoptotic proteins, regulates mitochondrial apoptosis [75]. Furthermore, PON2 influences the expression of drug transporters, particularly those belonging to the ABC family [76]. P-glycoprotein (an ABC transporter), is responsible for the efflux of chemotherapeutic agents from cancer cells and is a significant contributor to drug resistance [77]. PON2 modulates P-glycoprotein expression, promotes drug efflux, resulting in the reduction of intracellular concentrations of chemotherapeutic agents, and

increases drug resistance [78]. The enzymatic activity associated with PON2, including paraoxonase, arylesterase, and lactonase which plays crucial roles in detoxifying chemotherapeutic agents, thus reducing their efficacy [22, 42, 79]. Paraoxonase activity has been shown to exert a protective effect against cisplatin by neutralizing its toxic metabolites, whereas arylesterase and lactonase contribute to the metabolism and clearance of platinum-based drugs, thereby reducing their cytotoxicity [42, 79]. PON2's influence on the cytochrome P450 enzyme located in the endoplasmic reticulum, which is responsible for drug metabolism, affects the breakdown and clearance of chemotherapeutic agents, potentially diminishing their therapeutic efficacy [42, 80]. Cytochrome P450 enzymes are crucial for drug detoxification and for maintaining physiological equilibrium. They metabolize a wide range of drugs and xenobiotics, significantly contributing to drug elimination and influencing drug efficacy [81, 82].

In conclusion, PON2's multifaceted role in cancer cells (Figure 2), ranging from modulating oxidative stress and apoptotic pathways to affecting drug metabolism and efflux, contributes significantly to chemotherapy resistance. By maintaining the redox balance and altering cellular responses to chemotherapeutic agents, PON2 enhances cancer cell survival and reduces treatment effectiveness.

## 5 | Crosstalk Between Chemotherapy and Radiotherapy Resistance

The intricate crosstalk between chemotherapy and radiotherapy resistance is mediated by PON2, which plays a crucial role in enhancing cancer cell survival through multiple mechanisms. PON2's antioxidant properties are fundamental in mitigating oxidative stress and preserving cellular integrity, thereby reducing the efficacy of chemotherapeutic agents [42]. By scavenging ROS and modulating glutathione levels, PON2 diminishes oxidative damage, impedes DNA damage checkpoints, and promotes repair pathways, thereby fostering resistance to chemotherapy [63, 64]. Similarly in radiotherapy, PON2 plays a crucial role in counteracting radiation-induced stress [73]. Its presence in the endoplasmic reticulum and mitochondria facilitates antioxidant defenses, alleviates endoplasmic reticulum stress, and regulates calcium homeostasis, thereby reducing apoptosis. PON2 also influences the Wnt/β-catenin and PI3K-AKT signaling pathways, enhancing DNA repair and cellular survival in response to radiation [35, 40]. By stabilizing critical repair proteins such as ATM/ATR and modulating signaling cascades such as NF-κB and MAPK/ERK, PON2 further contributes to radiotherapy resistance [11]. These overlapping mechanisms (Figure 3) emphasize PON2's central role in both chemotherapy and radiotherapy resistance, showing how its antioxidant and anti-apoptotic functions, along with its influence on DNA repair and cell survival pathways can help cancer cells evade multiple forms of therapeutic intervention [23, 42]. However, OSCC resistance is more intricate and encompasses multiple mechanisms in addition to PON2. Cancer stem cells contribute to drug resistance through self-renewal and drug efflux processes. The epithelial-mesenchymal transition facilitates invasion and resistance to apoptosis [83]. Autophagy supports cellular survival under treatment-induced stress, whereas hypoxia-induced HIF activation diminishes therapy efficacy [84]. Dysregulated apoptosis and immune evasion (e.g., PD-L1 upregulation) contribute to resistance [85]. These factors underscore PON2's distinct role in OSCC resistance to treatment.

## 6 | Clinical Implications and Future Perspectives

PON2 has emerged as a promising target for the improvement of OSCC treatment, as it helps cancer cells resist common

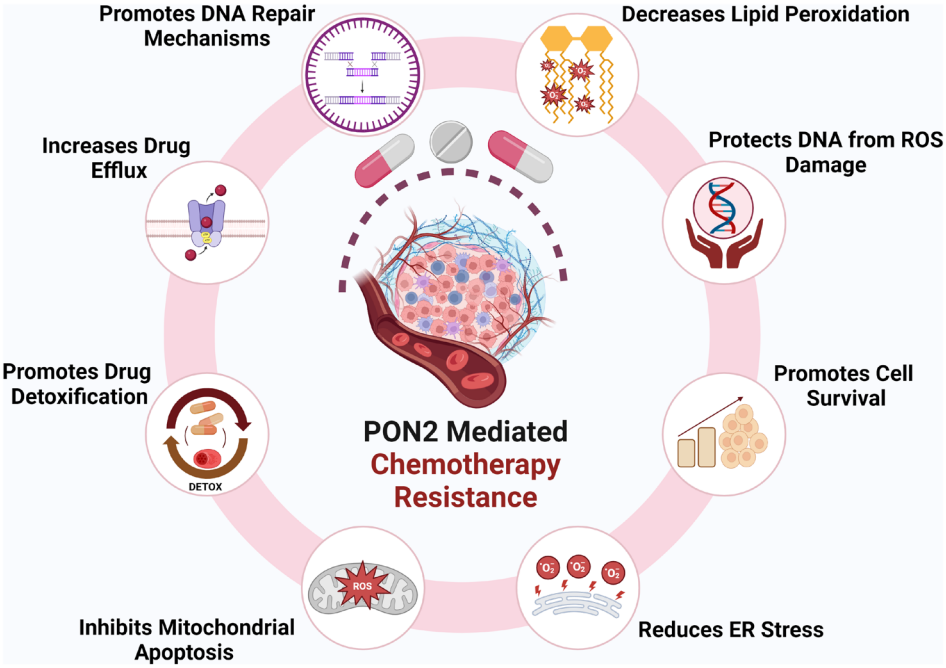


**FIGURE 2** | PON2 plays a crucial role in resistance to chemotherapy by mitigating oxidative stress, regulating apoptotic pathways, and modulating drug metabolism and efflux. Specifically, it protects cancer cells from reactive oxygen species (ROS)-induced damage, enhances cellular survival, promotes drug resistance, and reduces the therapeutic efficacy of chemotherapeutic agents.

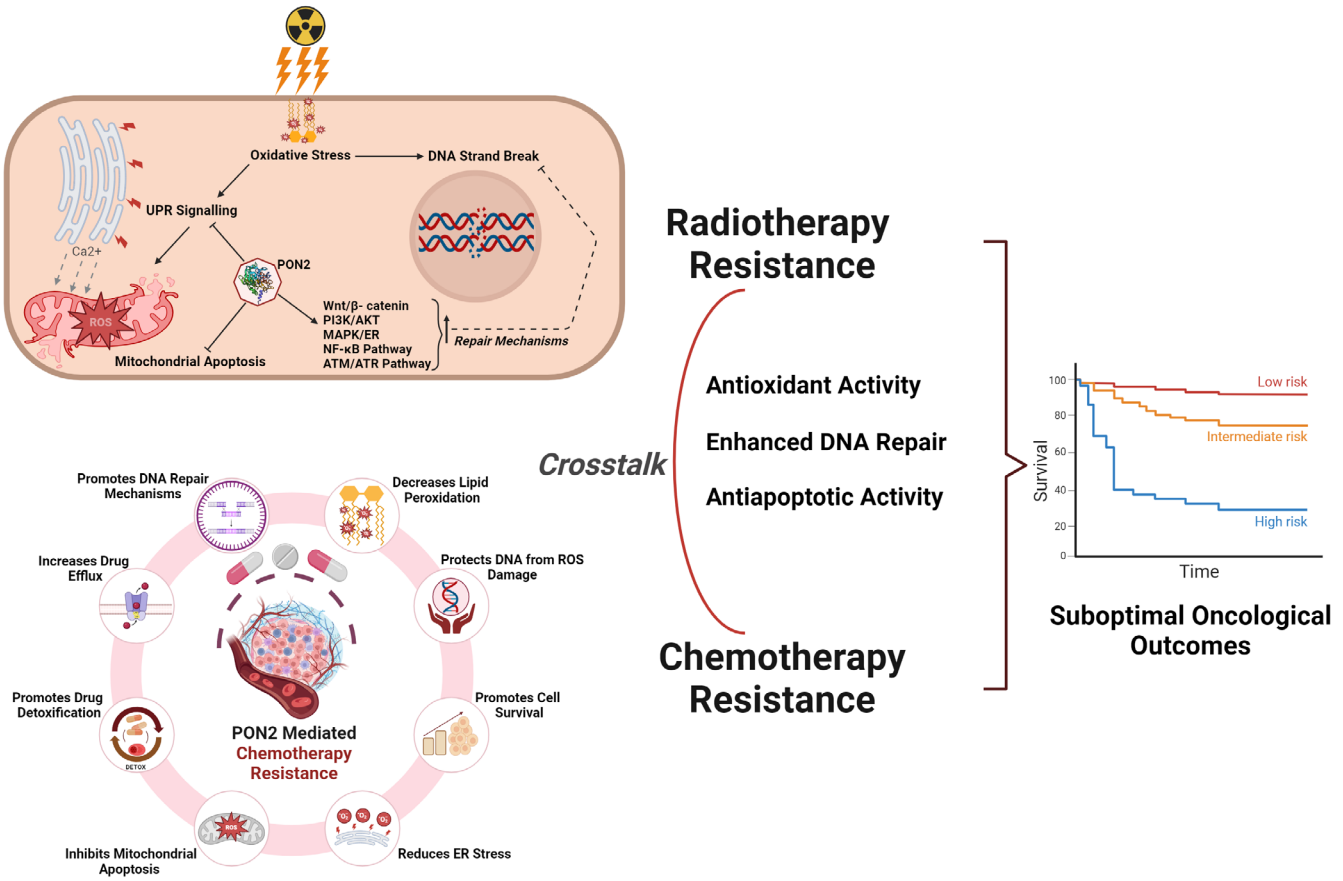


**FIGURE 3** | Crosstalk between chemotherapy and radiotherapy resistance.

treatments such as radiation and chemotherapy. The potential of PON2 as a therapeutic target is heightened by its overexpression in tumors and its crucial role under hypoxic conditions that are prevalent in the tumor microenvironment. Additionally, its capacity to facilitate chemoresistance has a significant impact on cancer treatment outcomes. By blocking PON2 (either by suppressing biosynthesis or antagonistic/allosteric inhibition), we can enhance the effectiveness of these therapies against OSCC. Research in exploring strategies to target PON2, including gene silencing, small-molecule drugs, and leveraging the immune system, is required. These efforts have a significant potential to improve the outcomes of patients with OSCC [86]. Moreover, PON2 has the potential to be used as a biomarker for predicting patient responses to treatment [11, 23, 42]. Measuring PON2 levels or activity could help clinicians customize treatment plans to suit each patient's unique profile, thereby improving the treatment outcomes. The development of PON2-targeting therapies encompasses the identification of PON2's role in diseases, the evaluation of potential drug candidates in preclinical studies, and the implementation of clinical trials to assess safety, efficacy, and dosing. Challenges in this process include the validation of biomarkers, addressing off-target effects, and managing disease heterogeneity. Furthermore, long-term safety concerns, regulatory hurdles, and the necessity for personalized treatment strategies complicate its translation into clinical practice. Innovations in molecular targeting, such as drug design and nanoparticle-based delivery, may pave the way to overcoming these obstacles. Bringing PON2 inhibition from research to practical treatment requires collaboration between pharmaceutical companies, researchers, and clinicians. Further studies are needed to understand how PON2 helps cancer cells resist radiation and chemotherapy. This includes investigating how PON2 interacts with other resistance mechanisms, such as cancer stem cells or immune evasion, and identifying the downstream effects and signaling pathways influenced by PON2. Targeting PON2 offers a promising strategy to overcome resistance in OSCC, and using PON2 as a biomarker while developing effective inhibitors is crucial for advancing precision medicine in OSCC treatment.

## 7 | Conclusion

This review emphasizes the fundamental role that PON2 plays in mediating resistance to chemotherapy and radiotherapy in patients with OSCC. By elucidating the complex molecular mechanisms by which PON2 confers a survival advantage to cancer cells, this review highlights its potential as a therapeutic target. Although significant progress has been made, further research is necessary to fully comprehend the complete spectrum of PON2's influence on the progression of OSCC and treatment response. A comprehensive understanding of PON2's interactions between the tumor microenvironment, cancer stem cells, and emerging therapeutic modalities is crucial for developing effective targeted therapies. Additionally, clinical studies are required to validate PON2 as a prognostic biomarker and assess the efficacy of PON2 inhibition in improving patient outcomes. Ultimately, a multidisciplinary approach that encompasses

basic, translational, and clinical research is essential to harness the full potential of targeting PON2 in the management of OSCC.


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### Ethics Statement

The authors have nothing to report.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The authors have nothing to report.

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