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# The dual role of lncRNA-mRNA regulatory network in reshaping the tumor microenvironment and radiotherapy response in pancreatic ductal adenocarcinoma

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► ***Original article***

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## ABSTRACT

***Background:*** Pancreatic ductal adenocarcinoma (PDAC) is recognized as an exceptionally aggressive malignancy with limited treatment options. Radiotherapy, particularly creotactic body radiotherapy, plays a vital role in cancer management but faces challenges due to the complex microenvironment of tumors and intrinsic resistance mechanisms. ***Materials and Methods:*** Transcriptomic data from PDAC tissue samples were analyzed pre- and post-stereotactic body radiotherapy to identify variations in the expression of lncRNAs and mRNAs. Additionally, bioinformatics approaches were used to explore their interactions, focusing on the effects on p53-mediated apoptosis and immune cell dynamics, and to assess their potential as biomarkers for radiotherapy outcomes. ***Results:*** Genes linked to p53-driven apoptosis and DNA damage response showed significant upregulation after stereotactic body radiotherapy, highlighting the cytotoxic effects of radiotherapy. Conversely, immune-related genes were downregulated, indicating an immunosuppressive tumor microenvironment following radiotherapy. Meanwhile, co-expression analysis revealed a regulatory network between lncRNAs and mRNAs that influence radiotherapy-induced cytotoxicity and immunosuppression. Lastly, a risk model was constructed by incorporating three mRNAs (HSPA1L, MT-CYB, PMAIP1) and five lncRNAs (AC018816.3, RP11-147L13.2, CTD-2651B20.6, RP11-422P24.10, AC067945.4) to predict radiotherapy outcomes. ***Conclusion:*** This study uncovers the intricate interaction between lncRNAs and mRNAs in PDAC, especially in the context of radiotherapy. Our results demonstrated that the lncRNA-mRNA network significantly impacts the tumor microenvironment and radiotherapy response by regulating pathways involved in cell death and immunosuppression. Thus, targeting this network could enhance radiotherapy efficacy and mitigate its immunosuppressive effects, offering novel strategies to improve the treatment outcomes of PDAC.

## INTRODUCTION

PDAC is recognized as a highly aggressive and fatal forms of cancer, characterized by its asymptomatic progression, late diagnosis, and high resistance to current treatment modalities [1]. The limited effectiveness of existing treatments, such as chemotherapeutic and targeted approaches, highlights the urgent need for innovative strategies and deeper insights into the disease's molecular mechanisms [2]. This gap highlights the urgency of identifying novel targets and mechanisms underlying PDAC progression and treatment resistance.

Radiotherapy (RT) is a pivotal component of the multimodal treatment approach for PDAC, particularly crucial for individuals with advanced or inoperable tumors [3]. Among RT modalities, stereotactic body radiotherapy (SBRT) has shown substantial potential in treating pancreatic cancer by precisely targeting the tumor with high-dose radiation while reducing harm to surrounding healthy tissues [4]. However, despite being pivotal, the efficacy of RT in PDAC is limited by intrinsic resistance mechanisms within the tumor and the complex interactions within the dense stromal environment of the tumor microenvironment (TME), which significantly affect treatment outcomes. Furthermore, the heterogeneity of tumor responses to SBRT varies; while some exhibit a substantial reduction in size, others may demonstrate resistance [5]. Indeed, addressing these challenges is vital for enhancing survival outcomes and the well-being of PDAC patients, highlighting the need for ongoing research and clinical trials to pioneer new approaches and technologies to improve RT effectiveness in PDAC treatment [6].

The tumor microenvironment in PDAC is marked by a robust desmoplastic reaction, forming a complex network of cancer cells, fibroblasts, immune cells, and a dense extracellular matrix. This unique environment not only drives tumor growth and metastasis but also plays a central role in mediating



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resistance to therapies, including RT [7, 8]. The interplay between PDAC cells and the TME promotes an immunosuppressive state, thereby contributing to tumor aggressiveness and presenting significant barriers to effective drug delivery and treatment efficacy [9]. Targeting the TME and disrupting these interactions hold the potential for sensitizing PDAC tumors to various treatments, including RT, thereby enhancing therapeutic outcomes. Unraveling the mechanisms by which the TME supports PDAC's resistance to therapies is crucial for advancing more effective treatment strategies.

Recent cancer research identified the lncRNA-mRNA regulatory network as a pivotal factor influencing progression, metastasis, and treatment response in cancers like PDAC [10]. This network can modulate critical cellular pathways, including those controlling survival, growth, and immune escape, thereby significantly influencing disease progression and responses to treatments such as RT [11]. However, despite such promising findings, the precise roles and mechanisms through which the lncRNA-mRNA network impacts the TME and RT response in PDAC remain largely unexplored. This gap in our understanding represents a significant obstacle in leveraging this network for clinical benefit. Addressing this gap could open avenues for discovering new therapeutic targets and developing innovative strategies, potentially improving the effectiveness of current treatments and offering renewed hope for PDAC therapy [12, 13].

This study focused on exploring the dual functions of the lncRNA-mRNA regulatory network in shaping the TME and modulating responses to SBRT in PDAC. By investigating the mechanisms by which this network influences SBRT-induced cytotoxicity through cell death pathways and immune responses while concurrently promoting an immunosuppressive TME, this study sought to uncover the mechanisms underlying treatment resistance and identify biomarkers predictive of treatment outcomes. Furthermore, this research examined strategies to manipulate the lncRNA-mRNA network to enhance SBRT sensitivity and counteract therapeutic resistance in PDAC. As far as we know, this is the first comprehensive study to elucidate the dual role of the lncRNA-mRNA regulatory network in reshaping the TME and modulating the response to SBRT in PDAC. Unlike earlier research that mainly examined either the effects of SBRT on tumor cells or the role of individual lncRNAs, this research integrated transcriptomic data to assess the effect of the interplay between lncRNAs and mRNAs on both cell death pathways and immune evasion mechanisms. Furthermore, a novel risk model was constructed based on this lncRNA-mRNA network, which showed promise as a predictive tool for radiotherapy outcomes. In summary, this research not only enhances our understanding of the molecular basis of radiotherapy resistance in PDAC but also introduces new opportunities for targeted therapeutic strategies to improve treatment effectiveness.

## MATERIALS AND METHODS

### *Collection and analysis of publicly available data*

Publicly available RNA sequencing data comprising 21 samples from the GSE185311 dataset were retrieved from the Sequence Read Archive (SRA). This dataset included samples from 9 SBRT-treated PDAC patients and 12 untreated controls. All patients were diagnosed with resectable pancreatic head adenocarcinoma based on NCCN guidelines. Participants were required to be 18 years or older, with no signs of metastasis or involvement of major blood vessels, and Karnofsky performance status >70. Treated patients underwent SBRT at a cumulative dose of 25 Gy, administered in five fractions, followed by pancreaticoduodenectomy approximately 7 days later. Untreated patient data were used for comparison. Detailed demographic information, including age, gender, and clinical characteristics, can be accessed in the original publication associated with the dataset [14].

The SRA Run files were converted into FASTQ format utilizing the fastq-dump function from the NCBI SRA Toolkit (v2.9.6). The raw sequencing data then underwent quality filtering to remove low-quality bases with the fastp tool (v0.23.4) [15]. Finally, the processed reads were assessed for quality using FastQC (v0.12.1).

### *Alignment of reads and identification of differentially expressed genes (DEGs)*

The cleaned reads were mapped to the human reference genome with HISAT2 (v2.2.1) [16], with only uniquely mapped reads considered for gene quantification and the calculation of Fragments per Kilobase of transcript per Million mapped reads (FPKM). Differential expression analysis was conducted with DESeq2 (v1.42.0) [17] on raw count data to identify differentially expressed genes (DEGs), with significant changes defined by a fold change (FC) ≥2 or ≤0.5 and a false discovery rate (FDR) ≤0.05.

### *Novel lncRNA prediction*

RNA sequencing data were grouped using StringTie (v2.1.7) [18] and screening for expressed transcripts using the criterion FPKM ≥1. Then, StringTie was used to merge these transcripts into a single GTF file. Four software tools, namely CPC2 [19], LGC [20], CNCI [21] and CPAT [22], were applied for lncRNA prediction. Transcripts were removed if they overlapped coding genes, were shorter than 200 bp, had coding potential, or were within 1000 bp of a neighboring gene, resulting in the identification of novel lncRNA candidates.



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### *Co-expression analysis*

Pearson's correlation was used to examine the regulatory links between lncRNAs and their target genes. Correlations with an absolute Pearson's correlation of ≥0.6 and a p-value ≤0.01were selected for further analysis and interpretation.

### *Functional enrichment analysis*

Functional enrichment analysis was carried out using the clusterProfiler package (v4.6.2) [23] to identify enriched Gene Ontology (GO) terms and KEGG pathways.

### *Cell-type quantification*

To assess the immune and stromal cell composition in the PDAC TME, two computational approaches, namely xCell (v1.3) [24] and ESTIMATE (v1.0.13), were adopted [25].

### *Establishment of the risk assessment model*

A risk model was constructed using the TCGA pancreatic adenocarcinoma (PAAD) dataset. Univariate Cox regression identified genes with prognostic value (P<0.05), followed by LASSO-penalized Cox regression to refine the gene set, utilizing the "survival" and "survminer" R packages [26]. Gene coefficients were calculated using multivariate Cox regression, and patients were categorized into high- and low-risk groups based on their risk scores, computed as Σ(Ci × EXPi). The survival differences between these groups were analyzed using the "survival" package, and the prognostic accuracy of the risk signature was assessed using the 'timeROC' package [27].

### *Other statistical analysis*

Principal component analysis (PCA) was performed using the factoextra package in R (v1.0.7) to visualize sample clustering. Heatmaps of the clustered data were generated using the pheatmap (v1.0.12) package in R.

## RESULTS

### *Immune cell infiltration dynamics post-stereotactic radiotherapy in PDAC tissues*

The GSE185311 transcriptomic dataset was used to investigate the immune cell landscape in PDAC tissues and assess the effects of SBRT. The dataset included 13 non-treated PDAC tissue samples as controls and 9 post-SBRT patient samples. This comprehensive analysis aimed to unravel the impacts of radiotherapy on both immune cell composition and gene expression in PDAC tissues (figure 1A). The ESTIMATE algorithm was applied to evaluate tumor purity and calculate stroma, immune, and ESTIMATE scores, as well as tumor purity. Our findings revealed a significant decrease in immune cell infiltration in the SBRT-treated cohort compared to the controls. Notably, the analysis indicated that the stromal elements and overall tumor purity were comparable between the two groups post-treatment (figure 1B).

Further stratification of immune cell types using xCell demonstrated a significant decline in the proportions of endothelial cells, naïve B cells, memory B cells, total B cells, central memory CD4+ T cells, memory CD4+ T cells, and effector memory CD4+ T cells post-SBRT (figure 1C). This pattern indicates a targeted effect of early-stage radiotherapy on immune populations, with notable reductions in specific subsets, such as regulatory T cells (Tregs) and activated myeloid dendritic cells. These observations collectively point to a dynamic shift in the immune landscape of PDAC tissues following radiotherapy, with potential implications for optimizing therapeutic strategy and patient outcomes.

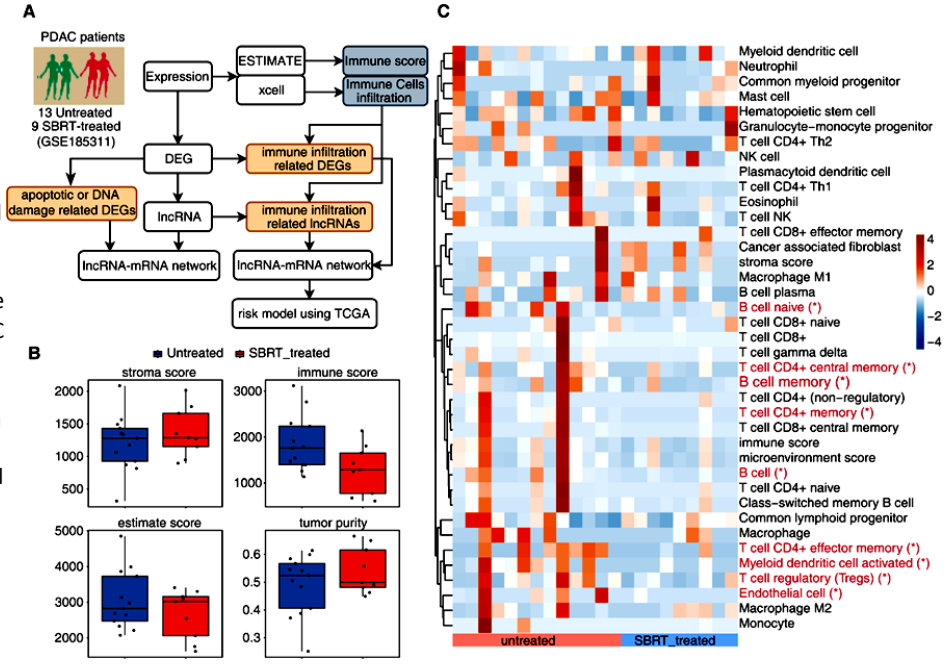


**Figure 1.** Immune cell infiltration dynamics post-stereotactic radiotherapy in PDAC tissues. **(A)** Overview of the study design and analytical approach to investigate the impact of SBRT on immune cell dynamics in PDAC tissues. **(B)** Boxplot illustrating changes in tumor purity, stromal, and immune scores between SBRT-treated PDAC tissues and untreated controls, calculated using the ESTIMATE algorithm. **(C)** Heatmap depicting a significant decrease in the proportions of specific immune cell types, including central memory CD4+ T cells, naive B cells, and memory B cells, among others, after SBRT treatment.



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***Radiotherapy elevates p53-mediated apoptotic and DNA damage genes while suppressing immune -related gene expression***

To elucidate the impact of SBRT on gene expression profiles in PDAC tissues, a detailed co-expression analysis was conducted on the differentially expressed mRNAs, focusing on their association with immune cell dynamics. The analysis yielded 242 mRNAs exhibiting differential expression post-SBRT treatment compared to controls. Among them, 103 mRNAs were up-regulated, whereas 139 were down-regulated, suggesting a distinct shift in gene expression following radiotherapy. GO Biological Process (GO-BP) enrichment analyses were conducted to determine the functional implications of these changes (figsure 2A-B).

The up-regulated mRNAs in the SBRT-treated group were predominantly enriched in pathways associated with intrinsic apoptotic signaling, especially those mediated by p53, including signal transduction by p53 class mediators, regulation by calcium ions, and DNA damage-induced apoptosis (figure 2A). These results align with previous studies, corroborating the hypothesis that radiotherapy enhances the DNA damage response, thereby amplifying gene expression associated with apoptotic pathways. Conversely, the down-regulated mRNAs were largely linked to antigen receptor-mediated signaling pathways, cellular surface receptor signaling pathways associated with immune activation and regulation, and other immune-related functions such as activation of B cells and differentiation of lymphocytes (figure 2B). This finding implies that SBRT inhibits immune activation and response capabilities post-radiotherapy.

In total, 8 up-regulated genes (PRODH, PHLDA3, EDA2R, RRM2B, MDM2, RPS27L, BBC3, and CDKN1A) were involved in apoptosis and DNA damage (figure 2C). At the same time, the 18 downregulated genes were involved in immune-related pathways (figure 2D). Taken together, these observations signal that SBRT has a dual impact on PDAC tissues: it not only promotes pathways conducive to apoptosis but also suppresses certain aspects of the immune response.

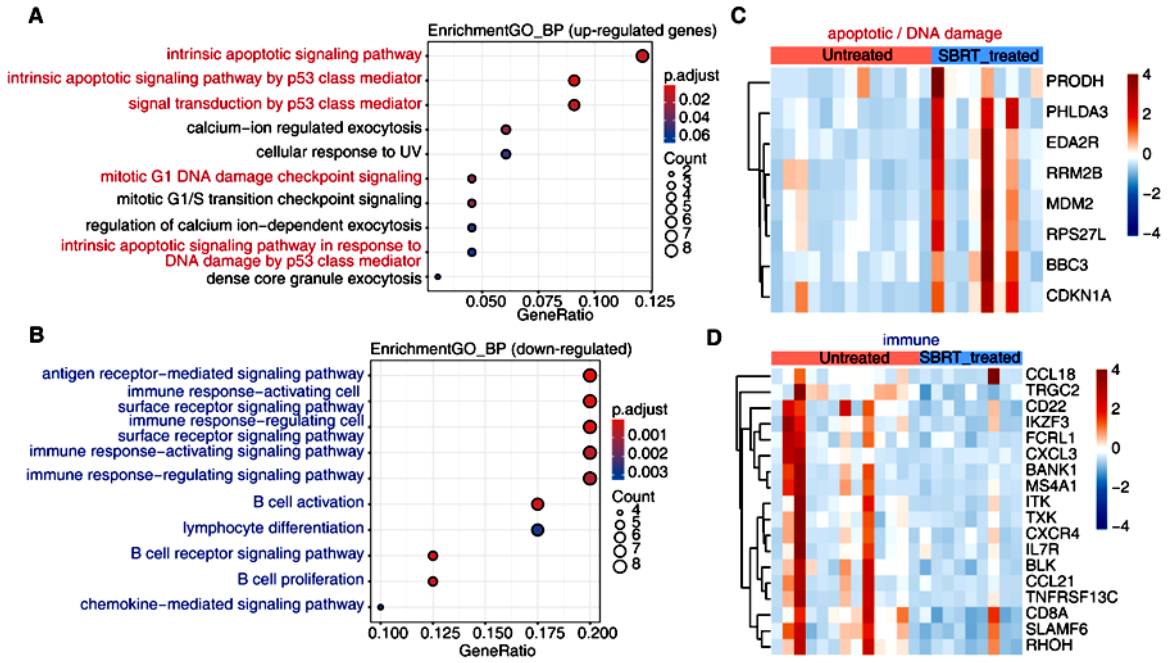


**Figure 2.** Radiotherapy elevates p53-mediated apoptotic and DNA damage genes while suppressing immune-related gene expression. **(A-B)** Enrichment analysis of up-regulated and down-regulated mRNAs in SBRT-treated PDAC tissues. Figure 2B focuses on pathways related to intrinsic apoptotic signaling and DNA damage response, while Figure 2C highlights suppressed pathways involved in immune cell activation and signaling. **(C-D)** Expression heatmaps of the top 10 pathways affected by radiotherapy, separated into those associated with apoptosis and DNA damage **(C)** and immune function **(D)**.

***Radiotherapy induces dynamic lncRNA expression and modulates apoptotic and DNA damage-related pathways in PDAC***

LncRNAs play pivotal roles in mediating gene expression, typically through cis or trans mechanisms to influence their target entities. Given their canonical functions, the connections between differentially expressed lncRNAs (DElncRNAs) and their putative target genes were examined. Among the 15,280 identified known lncRNAs, 14,566 were shared between the two groups. Interestingly, 541 lncRNAs were unique to the control group, whereas 173 were specific to the radiotherapy-treated samples. Moreover, 3,208 novel lncRNAs were identified, with 3,015 being shared between the two groups, 133 specific to the control group, and 60 unique to the radiotherapy group.

To display the expression of lncRNAs across these groups, differentially expressed lncRNAs (DElncRNAs) were analyzed. Additionally, a co-expression network was constructed for differentially expressed lncRNAs and apoptotic and DNA damage-


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related mRNAs (figure 3A). The lncRNA GS1-279B7.2 potentially downregulates EDA2R. Following radiotherapy, the expression level of GS1-279B7.2 significantly decreased, whereas that of EDA2R significantly increased. Lower expression levels of GS1-279B7.2 are associated with a better prognosis. Likewise, higher expression levels of EDA2R are linked to improved outcomes (figure 3B-C). These results emphasize the importance of radiotherapy in cancer therapy and the potential for lncRNA-targeted interventions for enhancing therapeutic efficacy.

### *LncRNA-mRNA-Immune cell network establishment and risk model construction*

Here, we constructed a lncRNA-mRNA-immune cell network via co-expression analysis to subsequently develop a prognostic risk model. To construct the lncRNA-mRNA-immune cell network, differentially expressed mRNAs and lncRNAs significantly associated with immune cells were initially isolated. Thereafter, a co-expression analysis was performed to build the lncRNA-mRNA network, linking the mRNAs to their GO-BP functions (figure 4A).

Using the results from pathway enrichment analysis, the TCGA PAAD dataset was analyzed using univariate Cox regression and LASSO regression to assess expression levels within the lncRNA-mRNA network and develop a risk score associated with overall survival and clinical features. A total of eight critical genes were identified, comprising three mRNAs (HSPA1L, MT-CYB, and PMAIP1) and five lncRNAs (AC018816.3, RP11-147L13.2, CTD-2651B20.6, RP11-422P24.10, and AC067945.4) (figure 4B). As expected, the risk model revealed that strong correlations were observed between the expression of high-risk genes or lncRNAs and decreased patient survival, underscoring their prognostic significance (figure 4C). Furthermore, receiver operating characteristic (ROC) curve analysis was performed on the TCGA cohort to evaluate the predictive accuracy of the developed model (figure 4D). Additional analysis of PDAC patient data from the TCGA database revealed that high expression levels of HSPA1L and lncRNA RP11-422P24.10 were associated with superior survival outcomes, thereby validating their role as potential prognostic markers (figure 4E). Notably, the expression levels of lncRNA RP11-422P24.10 and HSPA1L were lower post-SBRT, suggesting a possible adverse impact of radiotherapy on these markers (figure 4F). These results expanding our understanding of the complex lncRNA-mRNA-immune cell interactions, providing new perspectives on the molecular mechanisms driving PDAC progression and response to therapy. Consequently, the risk model based on this network may assist in predicting patient outcomes, thereby facilitating informed therapeutic decisions and enabling the formulation of personalized treatment plans.

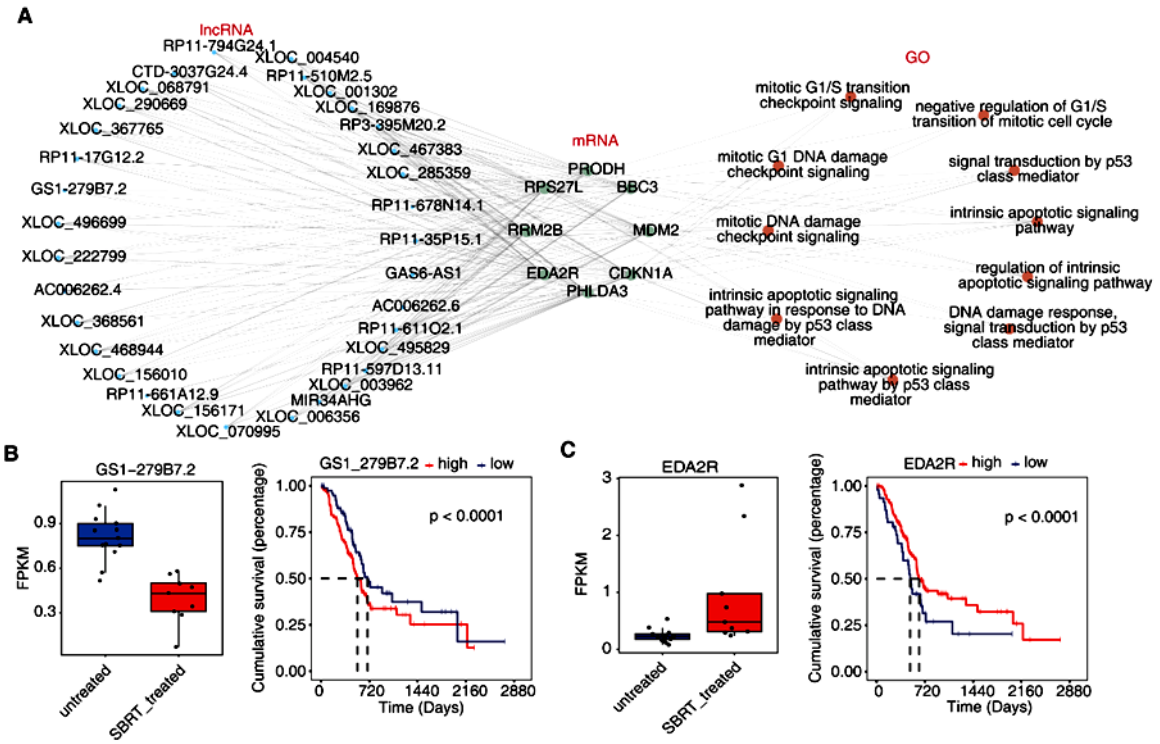


**Figure 3.** Radiotherapy induces dynamic lncRNA expression and modulates apoptotic and DNA damage-related pathways in PDAC. **(A)** Co-expression analysis of DElncRNAs and apoptotic and DNA damage-related DEGs. Co-expression pairs were identified using cutoffs of p-value ≤ 0.01 and |Pearson coefficient| ≥ 0.6. **(B)** Boxplot in the left panel illustrating the expression level (FPKM) of the lncRNA GS1-279B7.2. *: p-value ≤ 0.05; **: p-value ≤ 0.01; ***: p-value ≤ 0.001. Kaplan-Meier curves on the right panel depicting the overall survival of PAAD patients using kmplot online tools based on expression levels of GS1-279B7.2. **(C)** Similar analysis as in B, except using the gene EDA2R.



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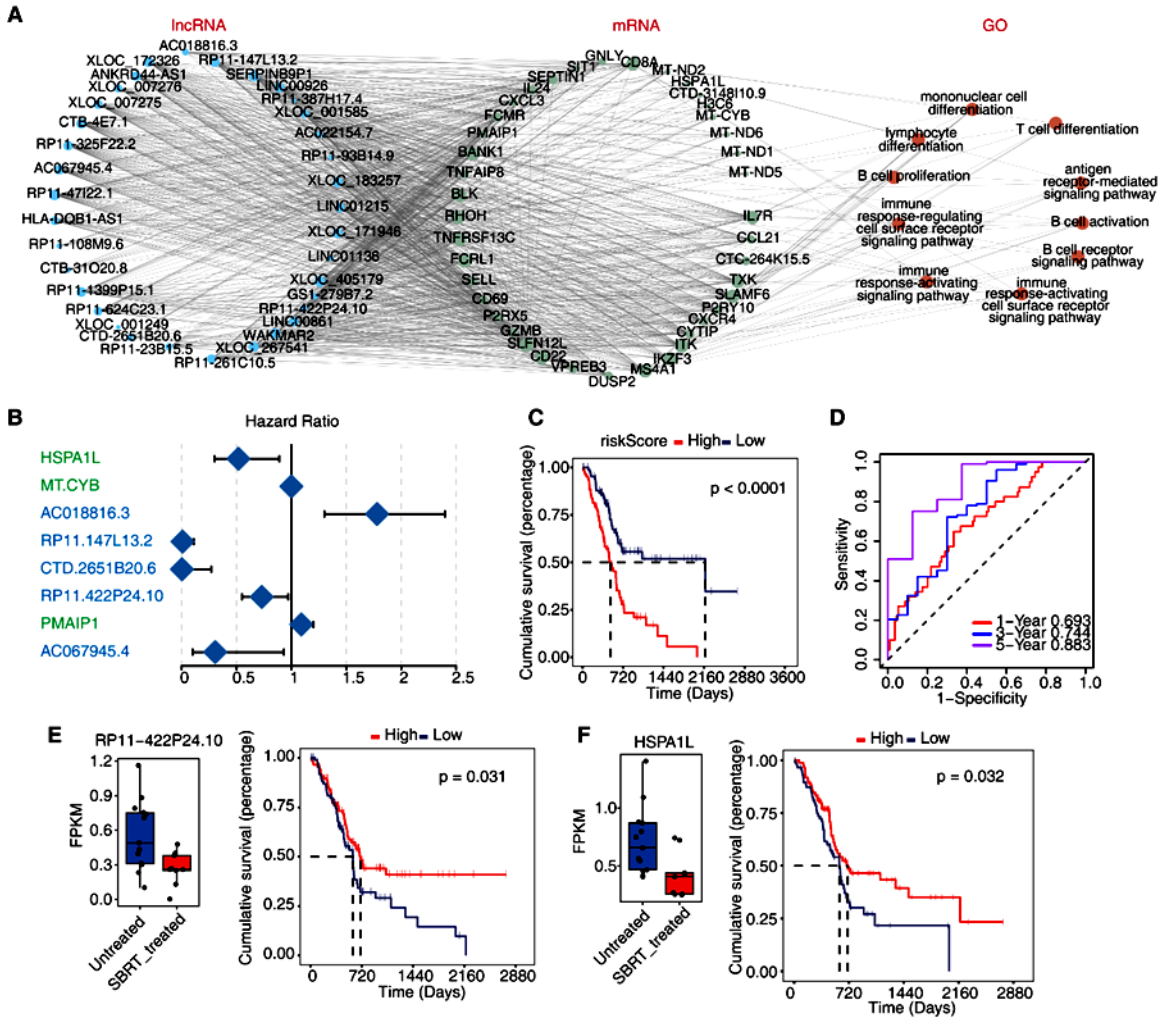


**Figure 4.** Establishment of the lncRNA-mRNA-immune cell network and risk model construction. **(A)** Co-expression analysis of DElncRNAs and DEGs correlated with changes in immune cell proportions. Co-expression pairs were identified using cutoffs of p-value ≤ 0.01 and a |Pearson correlation coefficient| ≥ 0.6. **(B)** Univariate Cox regression analysis identifying pivotal genes and lncRNAs associated with overall survival and clinical characteristics. **(C)** Risk assessment analysis presenting the association between high-risk gene or lncRNA expression and reduced patient survival, highlighting their prognostic significance. **(D)** Time-dependent ROC analysis was used to assess the performance of the risk model in predicting the 1-, 3- and 5-year survival of PAAD patients. Boxplot in the left panel showing the expression level (FPKM) of lncRNA RP11-422P24.10. *: p-value ≤ 0.05; **: p-value ≤ 0.01; ***:p-value ≤ 0.001. Kaplan-Meier curves in the right panel depicting the overall survival of PAAD patients using kmplot online tools based on the expression levels of RP11-422P24.10. **(F)** Similar to E, except using the gene HSPA1L.

## DISCUSSION

This investigation elucidated the bidirectional influence of the lncRNA-mRNA regulatory network on the TME and its impact on the responsiveness to radiotherapy in PDAC. A detailed analysis of transcriptomic alterations following SBRT revealed an upregulation of genes critical to p53-mediated apoptosis and DNA damage response pathways, demonstrating the direct cytotoxic influence of radiotherapy on tumor cell survival. Simultaneously, significant downregulation of immune-related genes was observed, indicative of radiotherapy-induced immunosuppression in the TME. This balance between promoting tumor cell death and limiting immune responses displays the complex equilibrium maintained by radiotherapy in PDAC management, demonstrating the mechanisms underlying radiotherapy's effectiveness and potential resistance. Overall, this study lays a theoretical reference for targeting precise elements within the lncRNA-mRNA network, thereby optimizing treatment approaches by enhancing the efficacy of radiotherapy and concurrently minimizing its immunosuppressive side effects.

The alterations in immune cell dynamics following SBRT in PDAC highlight the intricate relationship between RT and the tumor immune microenvironment. The down-regulation in immune cell-related gene expression suggests a shift towards an immunosuppressive TME, an established challenge in achieving effective cancer therapy. This dual effect of RT, which includes both the direct cytotoxic impact on tumor cells and the modulation of the immune microenvironment, is in agreement with existing literature on RT-induced


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immunomodulation. For instance, RT primed cytotoxic T cells in preclinical models of PDAC by driving immunogenic tumor cell death, indicating a potential to bolster antitumor immunity [14]. However, the enhanced antitumor immunogenicity could be counteracted by the buildup of immunosuppressive populations, including tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which inhibit T-cell activity and promote tumor progression [14]. To enhance treatment outcomes, future strategies may need to incorporate immunomodulating agents such as checkpoint inhibitors or metabolic pathway modulators that reprogram immune cells, thereby synergizing with RT to combat the immunosuppressive TME in PDAC.

The role of lncRNA-mRNA regulatory networks in modulating p53-mediated apoptosis and DNA damage response, particularly following radiotherapy in cancer, has garnered extensive attention recently. Many studies have demonstrated the significance of lncRNAs as crucial regulators within the p53 pathway, either enhancing or suppressing the function of p53 in apoptosis and DNA damage response. Mounting evidence suggests that genetic polymorphisms within lncRNA-p53 regulatory networks influence both the efficacy and toxicity of concurrent chemoradiotherapy, as documented in studies on nasopharyngeal carcinoma patients [28]. This highlights the potential of targeting lncRNAs in the p53 network to optimize therapeutic outcomes. Herein, lncRNAs directly interacted with proteins to modulate the p53 pathway, influencing cellular responses to radiotherapy. For instance, EDA2R, a member of the tumor necrosis factor (TNF) receptor superfamily, is transcriptionally induced by p53 and has been implicated in chemotherapy-induced alopecia, as noted in previous studies [29]. Similarly, Tanikawa et al. found that EDA2R, regulated by p53 in anoikis, indicating its potential role as a colorectal cancer tumor suppressor [30]. This research indicates that GS1-279B7.1 might be involved in the p53-mediated regulation of EDA2R, offering new insights into potential therapeutic targets. Thus, modulating these regulatory networks could enhance the sensitivity of cancer cells to radiotherapy and other treatments, offering promising avenues for improving treatment efficacy.

The dynamic interaction between lncRNA-mRNA regulatory networks and the tumor immune microenvironment is crucial in determining the efficacy of radiotherapy for cancer treatment. As integral components of the competing endogenous RNA (ceRNA) networks, lncRNAs are implicated in modulating diverse immune responses within the TME and are related to radiosensitivity [31, 32]. According to earlier studies, lncRNAs can suppress antitumor T cell activation, interfere with T cell homing, and recruit immunosuppressive cells, thus promoting an environment conducive to tumor growth, which may reduce the effectiveness of radiotherapy [33]. Additionally, integrative analyses in gastric cancer have identified key immune-related ceRNA regulatory axes, underscoring the link between specific lncRNA-mediated immune cell infiltration and cancer progression [34]. HSPA1L is key in cancer progression and the regulation of immune responses. Specifically, it enhances cancer stem cell-like characteristics by activating key signaling pathways that support stemness and therapy resistance, positioning it as an important target for cancer treatment and understanding tumor progression [35]. Furthermore, it may be regulated by the lncRNA RP11-422P24.10, whose expression is suppressed following radiotherapy, indirectly affecting the functionality of HSPA1L. Overall, these findings emphasize the pivotal influence of lncRNA-mRNA networks in the tumor immune microenvironment and their impact on radiotherapy outcomes. Strategically targeting particular lncRNAs within these networks offers a promising avenue for altering the tumor's immune landscape, thereby potentially enhancing radiotherapy efficacy and addressing resistance issues.

In summary, this study elucidates the dual function of the lncRNA-mRNA regulatory network in modulating both the tumor microenvironment and responses to stereotactic body radiotherapy in PDAC. Our findings deepen the understanding of radiotherapy resistance mechanisms and lay the groundwork for the development of more targeted therapeutic approaches. Future research should focus on validating these biomarkers in clinical settings to improve patient outcomes.

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***Author Contributions***: The authors confirm contribution to the paper as follows: study conception and design: J.W., Q.S.; data collection, analysis and interpretation of results: W.L., Y.L., and L.X.; draft manuscript preparation: W.L., J.Z.; revise of the menuscript: J.W., Q.S.. All authors reviewed the results and approved the final version of the manuscript.

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