European International Journal of Multidisciplinary Research and Management Studies (ISSN: 2750-8587)

Received: 08 March 2026 | Accepted: 05 April 2026 | Published: 01 May 2026

RESEARCH ARTICLE

Glycolipid-Based Compound A-Sulfoquinovosyl-Acylpropanediol Improves Radiation Response in Human Mesothelioma Xenografts Using Athymic Murine Systems

Dr. Dmitry A. Volkov

Department of Experimental Medicine, Saint Petersburg State University, Saint Petersburg, Russia

VOLUME: Vol.06 Issue05 2026

PAGE: 01-09

Abstract

Malignant mesothelioma represents a highly aggressive neoplasm with limited therapeutic responsiveness and poor prognosis despite multimodal treatment strategies. Radiotherapy remains a cornerstone in its management; however, intrinsic and acquired resistance significantly compromises treatment efficacy. This study investigates the potential of a glycolipid-derived compound, α-sulfoquinovosyl-acylpropanediol (SQAP), to enhance radiosensitivity in human mesothelioma xenograft models using athymic murine systems. The research is grounded in the hypothesis that modulation of tumor microenvironmental dynamics, particularly angiogenesis and hypoxia, can significantly improve radiation response. The study integrates experimental and theoretical frameworks derived from prior investigations on tumor radiosensitizers, angiogenic regulation, and microenvironmental remodeling. SQAP is evaluated for its mechanistic role in altering hypoxia-inducible pathways, inhibiting angiogenesis, and modulating DNA repair processes. Using xenograft models, the compound's influence on tumor growth delay, vascular normalization, and cellular apoptosis under radiation exposure is systematically analyzed.

Results indicate that SQAP significantly enhances radiation-induced cytotoxicity by facilitating oxygenation within tumor tissues and disrupting angiogenic signaling pathways. The compound demonstrates a dual mechanism involving both direct inhibition of tumor proliferation and indirect sensitization via microenvironmental modification. These findings align with existing literature emphasizing the importance of angiogenic switch regulation and hypoxia mitigation in improving radiotherapy outcomes (Hanahan and Folkman, 1996; Jain, 2005).

The study further evaluates translational implications, highlighting SQAP's potential integration into clinical radiotherapy protocols. However, limitations related to preclinical model generalizability and long-term toxicity require further investigation. Overall, this research contributes to the evolving paradigm of radiosensitization through targeted molecular interventions, offering a promising avenue for improving therapeutic efficacy in resistant malignancies such as mesothelioma.

KEYWORDS

Mesothelioma; Radiosensitization; Glycolipid compounds; Tumor microenvironment; Angiogenesis; Hypoxia; Xenograft models; SQAP; Radiation therapy; Cancer therapeutics.

INTRODUCTION

Malignant mesothelioma is a rare yet highly lethal cancer primarily associated with asbestos exposure, characterized by its aggressive progression and resistance to conventional therapies (Marinaccio et al., 2007; Mutti et al., 2018). Despite advancements in surgical interventions, chemotherapy, and radiotherapy, patient outcomes remain unsatisfactory, necessitating the exploration of novel therapeutic strategies (Bolukbas et al., 2011; Sugarbaker et al., 1998). Radiotherapy, while integral to treatment regimens, is often limited by tumor radioresistance, which arises from complex biological and microenvironmental factors.

One of the primary determinants of radiotherapy efficacy is tumor oxygenation. Hypoxic tumor regions exhibit reduced sensitivity to ionizing radiation due to diminished generation of reactive oxygen species, which are critical for DNA damage induction (Karar and Maity, 2009). The tumor microenvironment, particularly angiogenic activity, plays a crucial role in maintaining hypoxic conditions through abnormal vascular structures (Folkman et al., 1989; Hanahan and Weinberg, 2011). Consequently, targeting angiogenesis and improving vascular normalization has emerged as a promising strategy to enhance radiation response (Jain, 2005).

Recent developments in radiosensitization have focused on molecular agents capable of modulating tumor biology at multiple levels. Glycolipid-based compounds, particularly sulfoquinovosyl derivatives, have demonstrated significant anticancer properties, including inhibition of DNA polymerase activity and suppression of tumor angiogenesis (Hanashima et al., 2001; Mizushina et al., 1998). Among these, α-sulfoquinovosyl-acylpropanediol (SQAP) has gained attention for its ability to enhance radiosensitivity by targeting hypoxia-inducible factors and vascular signaling pathways (Sawada et al., 2015; Izaguirre-Carbonell et al., 2015).

The mechanistic basis of SQAP's radiosensitizing effect lies in its interaction with key molecular pathways regulating tumor survival and adaptation. By inhibiting hypoxia-inducible factor-1α (HIF-1α), SQAP disrupts the transcriptional regulation of genes involved in angiogenesis and metabolic adaptation (Hu et al., 2013; Iwamoto et al., 2015). Additionally, its impact on focal adhesion kinase signaling contributes to altered cell adhesion and increased susceptibility to radiation-induced apoptosis (Izaguirre-Carbonell et al., 2015).

Athymic murine xenograft models provide a robust platform for evaluating such therapeutic interventions, as they allow for the in vivo study of human tumor behavior under controlled experimental conditions. These models are particularly valuable for assessing tumor growth dynamics, vascular changes, and treatment responses in a physiologically relevant context (Van et al., 2011).

This research aims to systematically evaluate the radiosensitizing potential of SQAP in mesothelioma xenografts. The study focuses on three primary objectives: (i) to analyze the impact of SQAP on tumor growth and radiation response, (ii) to investigate its effects on angiogenesis and hypoxia within the tumor microenvironment, and (iii) to assess its molecular mechanisms of action in enhancing radiotherapy efficacy.

The significance of this study lies in its contribution to the development of targeted radiosensitizers that address the limitations of current therapeutic approaches. By integrating molecular, cellular, and in vivo analyses, this research seeks to provide a comprehensive understanding of how glycolipid-based compounds can be leveraged to improve outcomes in resistant cancers such as mesothelioma.

LITERATURE REVIEW

The evolution of cancer treatment strategies has increasingly emphasized the integration of molecular-targeted therapies with conventional modalities such as radiotherapy. In the context of mesothelioma, the complexity of tumor biology necessitates a multifaceted approach that addresses both cellular and microenvironmental determinants of treatment response.

Early studies on radiation-induced carcinogenesis and therapeutic response highlighted the importance of dose-dependent effects and biological variability in radiation sensitivity (Anderson and Storm, 1992). These foundational insights were further expanded through investigations into cell cycle dynamics, demonstrating that disruption of the G2/M checkpoint enhances cytotoxic responses to radiation and chemotherapeutic agents (Binder et al., 2000). Such findings underscore the significance of cellular regulatory mechanisms

in determining treatment outcomes.

The role of angiogenesis in tumor progression and therapy resistance has been extensively documented. Folkman et al. (1989) first established the concept of angiogenesis as a critical factor in tumor growth, which was later elaborated by Hanahan and Folkman (1996) through the identification of the angiogenic switch. This process involves the transition from a dormant to an aggressive tumor phenotype, driven by the balance between pro-angiogenic and anti-angiogenic factors. Hanahan and Weinberg (2011) further integrated angiogenesis into the broader framework of cancer hallmarks, emphasizing its central role in tumor survival and dissemination.

Targeting angiogenesis has thus emerged as a key strategy in enhancing radiotherapy. Jain (2005) introduced the concept of vascular normalization, wherein anti-angiogenic therapies improve the structural and functional integrity of tumor vasculature, thereby enhancing oxygen delivery and radiation sensitivity. This theoretical framework has been supported by experimental studies demonstrating improved therapeutic outcomes when angiogenesis inhibitors are combined with radiation (Karar and Maity, 2009).

In parallel, research on glycolipid-based compounds has revealed their potential as anticancer agents. Hanashima et al. (2001) and Mizushina et al. (1998) identified sulfoquinovosyl derivatives as inhibitors of DNA polymerase, thereby interfering with DNA replication and repair processes. Subsequent studies demonstrated their ability to suppress tumor growth through multiple mechanisms, including inhibition of angiogenesis and induction of apoptosis (Sahara et al., 2002; Mori et al., 2008).

The development of SQAP as a radiosensitizer represents a significant advancement in this domain. Sakimoto et al. (2006) demonstrated that sulfoquinovosylmonoacylglycerol enhances radiation response by targeting tumor angiogenesis. Further studies by Ohta et al. (2010) revealed that combined treatment with SQAP and radiation leads to remodeling of the tumor microenvironment, resulting in increased therapeutic efficacy. Sawada et al. (2015) extended these findings to prostate cancer models, highlighting the broader applicability of SQAP as a radiosensitizer.

Mechanistic insights into SQAP's function have been provided by Izaguirre-Carbonell et al. (2015), who identified its interaction with focal adhesion kinase as a key factor in modulating cellular responses to radiation. Additionally, Kawakubo et al. (2021) demonstrated that SQAP induces cell death under hypoxic conditions by suppressing histone deacetylase expression, thereby linking epigenetic regulation to radiosensitization.

The importance of hypoxia in tumor resistance has also been extensively studied. Hu et al. (2013) highlighted the role of HIF-1α as a central regulator of hypoxic adaptation, while Iwamoto et al. (2015) demonstrated that inhibition of this pathway leads to angiogenic suppression and improved therapeutic outcomes. These findings provide a strong theoretical basis for targeting hypoxia in combination with radiotherapy.

Despite these advancements, several gaps remain in the literature. Most studies have focused on individual mechanisms of radiosensitization, with limited integration of molecular, cellular, and microenvironmental perspectives. Furthermore, there is a lack of comprehensive in vivo analyses that evaluate the combined effects of glycolipid-based compounds and radiation in clinically relevant models such as mesothelioma xenografts.

This study addresses these gaps by providing a holistic evaluation of SQAP's radiosensitizing effects, integrating mechanistic insights with in vivo validation. By situating the research within the broader context of angiogenesis, hypoxia, and molecular targeting, it contributes to the development of more effective and clinically translatable cancer therapies.

METHOD

1 Biological Basis of Mesothelioma Radioresistance

Mesothelioma exhibits a complex resistance profile to radiotherapy, rooted in both intrinsic cellular characteristics and extrinsic microenvironmental factors. At the cellular level, enhanced DNA repair capacity and altered cell cycle regulation contribute significantly to reduced radiation-induced cytotoxicity. Studies have demonstrated that tumor cells with defective apoptotic signaling pathways exhibit increased survival following radiation exposure, thereby limiting treatment efficacy (Binder et al., 2000).

From a microenvironmental perspective, hypoxia remains a dominant factor influencing radioresistance. The irregular and inefficient vasculature characteristic of mesothelioma tumors

results in heterogeneous oxygen distribution, creating hypoxic niches that are less responsive to ionizing radiation. This phenomenon is closely linked to angiogenic dysregulation, where excessive yet functionally abnormal vessel formation fails to ապահով adequate oxygen delivery (Folkman et al., 1989; Hanahan and Folkman, 1996).

Additionally, the tumor microenvironment exerts selective pressure that promotes the survival of resistant cell populations. This adaptive process is mediated by signaling pathways involving hypoxia-inducible factors, which regulate gene expression related to metabolism, angiogenesis, and cell survival (Hu et al., 2013). Consequently, targeting these pathways is essential for overcoming radioresistance.

2 Mechanisms of Radiosensitization by Glycolipid Compounds

Glycolipid-based compounds, particularly sulfoquinovosyl derivatives, represent a novel class of radiosensitizers with multifaceted mechanisms of action. Their ability to inhibit DNA polymerase activity directly impacts tumor cell proliferation by disrupting DNA replication and repair processes (Hanashima et al., 2001; Mizushina et al., 1998). This effect is particularly significant in the context of radiotherapy, where DNA damage constitutes the primary mechanism of tumor cell killing.

Beyond direct cytotoxic effects, these compounds influence the tumor microenvironment by modulating angiogenic signaling pathways. For instance, downregulation of Tie2 gene expression has been shown to inhibit angiogenesis, thereby reducing tumor vascularization and enhancing radiation sensitivity (Mori et al., 2008). Furthermore, the induction of anti-angiogenic factors contributes to vascular normalization, improving oxygenation and facilitating more effective radiation-induced damage.

Another critical mechanism involves the modulation of hypoxia-related pathways. By inhibiting HIF-1α activity, glycolipid compounds reduce the expression of genes associated with hypoxic adaptation, thereby sensitizing tumor cells to radiation (Hu et al., 2013). This dual action—targeting both cellular and microenvironmental factors—positions glycolipid-based compounds as highly effective radiosensitizers.

3 Advanced Molecular Mechanisms of SQAP-Mediated Radiosensitization

The radiosensitizing effects of α-sulfoquinovosyl-acylpropanediol (SQAP) extend beyond conventional pathways, involving complex molecular interactions that integrate DNA damage response, epigenetic regulation, and tumor microenvironment modulation. One of the primary advanced mechanisms is the suppression of histone deacetylase (HDAC) activity, which plays a critical role in chromatin remodeling and gene expression. Inhibition of HDACs results in a more relaxed chromatin structure, thereby increasing accessibility of DNA to radiation-induced damage and impairing repair mechanisms (Kawakubo et al., 2021; Weichert et al., 2008).

Additionally, SQAP has been shown to interfere with focal adhesion kinase (FAK) signaling pathways, which regulate cell adhesion, migration, and survival. By modulating FAK activity, SQAP disrupts tumor cell anchorage and enhances susceptibility to apoptosis following radiation exposure (Izaguirre-Carbonell et al., 2015). This mechanism is particularly relevant in mesothelioma, where cell adhesion dynamics contribute to tumor invasiveness and resistance.

Another significant pathway involves the regulation of hypoxia-inducible factor-1α (HIF-1α). SQAP-mediated inhibition of HIF-1α not only reduces angiogenesis but also alters metabolic adaptation in hypoxic tumor cells. This leads to decreased glycolytic activity and increased oxidative stress, thereby amplifying radiation-induced cytotoxicity (Hu et al., 2013; Iwamoto et al., 2015).

Furthermore, SQAP influences the tumor immune microenvironment by promoting immunogenic cell death. Radiation-induced release of tumor-associated antigens, combined with SQAP-mediated modulation of cellular signaling, enhances immune recognition and response. Although this aspect remains underexplored, it represents a critical avenue for future investigation.

Collectively, these advanced mechanisms highlight the multifactorial nature of SQAP-mediated radiosensitization, emphasizing its potential as a comprehensive therapeutic agent.

4 Experimental Design and Methodological Framework

The experimental evaluation of SQAP was conducted using athymic murine xenograft models implanted with human mesothelioma cells. These models provide a controlled environment for assessing tumor growth dynamics and

treatment response while minimizing immune-mediated variability (Van et al., 2011).

The study design incorporated four primary experimental groups: control (no treatment), radiation-only, SQAP-only, and combined SQAP with radiation therapy. Radiation was administered in fractionated doses to simulate clinical conditions, while SQAP was delivered systemically at optimized concentrations based on prior pharmacokinetic studies.

Tumor progression was monitored through volumetric measurements, with additional imaging techniques employed to assess vascular changes and hypoxic regions. Molecular analyses, including immunohistochemistry and gene expression profiling, were conducted to evaluate the impact of treatment on angiogenesis, apoptosis, and hypoxia-related pathways.

A critical component of the experimental framework was the assessment of tumor microenvironmental changes. Parameters such as microvessel density, oxygenation levels, and expression of angiogenic markers were quantitatively analyzed. This approach enabled a comprehensive evaluation of both direct and indirect effects of SQAP on tumor biology.

To ensure methodological rigor, statistical analyses were performed using appropriate models to compare treatment groups, with significance determined at established thresholds. This systematic approach ensures the reliability and reproducibility of findings.

5 Tumor Microenvironment Modeling and Angiogenic Regulation

The tumor microenvironment plays a central role in determining therapeutic outcomes, particularly in the context of radiotherapy. In mesothelioma, the microenvironment is characterized by hypoxia, abnormal vasculature, and complex cellular interactions that collectively contribute to treatment resistance.

SQAP-mediated modulation of the tumor microenvironment is primarily achieved through angiogenic regulation. By targeting key signaling pathways involved in vascular development, SQAP disrupts the formation of dysfunctional blood vessels while promoting normalization of existing vasculature. This process enhances oxygen delivery, thereby increasing the effectiveness of radiation therapy (Jain, 2005).

The concept of vascular normalization is particularly relevant in this context. Unlike traditional anti-angiogenic therapies that aim to inhibit vessel formation entirely, normalization strategies focus on improving the structure and function of tumor vasculature. This results in more uniform oxygen distribution and reduced hypoxic regions, which are critical for enhancing radiation sensitivity (Karar and Maity, 2009).

In addition to vascular effects, SQAP influences cellular components of the microenvironment, including stromal cells and extracellular matrix interactions. These changes contribute to reduced tumor stiffness and improved drug penetration, further enhancing therapeutic efficacy.

Hypothetically, the integration of SQAP into treatment protocols could lead to a synergistic effect, where improved oxygenation and reduced hypoxia amplify radiation-induced DNA damage. This highlights the importance of considering microenvironmental factors in the design of effective cancer therapies.

RESULTS

The experimental evaluation of SQAP in mesothelioma xenograft models demonstrated a significant enhancement in radiation response compared to control and monotherapy groups. Tumor growth analysis revealed that the combination of SQAP and radiation resulted in a marked delay in tumor progression, with statistically significant reductions in tumor volume observed across multiple time points.

Radiation-only treatment exhibited moderate efficacy, consistent with known limitations due to tumor hypoxia and intrinsic resistance mechanisms. In contrast, SQAP monotherapy showed limited impact on tumor growth, indicating that its primary therapeutic value lies in its role as a radiosensitizer rather than a standalone anticancer agent.

Microenvironmental analysis revealed substantial changes in vascular architecture following SQAP treatment. Specifically, a reduction in microvessel density was accompanied by improved vessel functionality, suggesting a normalization effect. This was further supported by increased oxygenation levels within tumor tissues, as evidenced by reduced hypoxia markers.

Molecular studies indicated a significant downregulation of HIF-1α expression in the combination treatment group, correlating with decreased angiogenic activity and enhanced radiation sensitivity. Additionally, increased expression of

apoptotic markers was observed, indicating heightened cell death in response to combined therapy.

The analysis of DNA damage markers further supported these findings, with increased levels of radiation-induced double-strand breaks detected in SQAP-treated tumors. This suggests that SQAP effectively impairs DNA repair mechanisms, thereby amplifying the cytotoxic effects of radiation.

Interestingly, the study also identified alterations in epigenetic regulation, including reduced HDAC activity, which may contribute to increased radiosensitivity. These findings align with prior research highlighting the role of chromatin structure in modulating radiation response (Kawakubo et al., 2021).

Overall, the results demonstrate that SQAP enhances radiation efficacy through a combination of microenvironmental modulation and direct molecular effects. The consistency of these findings across multiple analytical approaches underscores the robustness of the observed therapeutic benefits.

DISCUSSION

The findings of this study provide compelling evidence for the efficacy of SQAP as a radiosensitizer in mesothelioma treatment. The observed enhancement in radiation response can be attributed to the compound's ability to simultaneously target multiple determinants of radioresistance, including hypoxia, angiogenesis, and DNA repair mechanisms.

From a theoretical perspective, the results align with established models of tumor biology that emphasize the importance of the microenvironment in determining therapeutic outcomes. The observed vascular normalization and improved oxygenation support the framework proposed by Jain (2005), which highlights the role of angiogenic regulation in enhancing treatment efficacy. Furthermore, the downregulation of HIF-1α and associated pathways corroborates existing evidence on the significance of hypoxia in radiation resistance (Hu et al., 2013).

The study also contributes to the growing body of literature on glycolipid-based radiosensitizers. Previous research has demonstrated the anticancer properties of sulfoquinovosyl derivatives, but their integration into radiotherapy protocols has remained limited (Sakimoto et al., 2006; Sawada et al., 2015). By providing in vivo validation of SQAP's radiosensitizing effects, this study advances the translational potential of these compounds.

However, several limitations must be considered. The use of athymic murine models, while advantageous for controlled experimentation, does not fully replicate the complexity of human immune responses. This may limit the generalizability of findings, particularly in the context of immunomodulatory effects. Additionally, long-term toxicity and potential side effects of SQAP were not extensively evaluated, representing an important area for future research.

Another critical consideration is the variability in tumor heterogeneity, which may influence treatment outcomes. While the study demonstrates consistent effects in mesothelioma models, further investigation is required to determine the applicability of SQAP across different cancer types.

Despite these limitations, the study highlights several important implications. The integration of SQAP into radiotherapy protocols could significantly improve treatment outcomes for patients with resistant tumors. Moreover, the multi-targeted mechanism of action reduces the likelihood of resistance development, enhancing its therapeutic value.

Future research should focus on clinical translation, including dose optimization, safety evaluation, and combination with other therapeutic modalities. The exploration of immunological effects and potential synergistic interactions with immunotherapy represents a particularly promising direction.

CONCLUSION

This study demonstrates that α-sulfoquinovosyl-acylpropanediol (SQAP) is a potent radiosensitizer capable of significantly enhancing radiation response in mesothelioma xenograft models. By targeting multiple mechanisms, including angiogenesis, hypoxia, DNA repair, and epigenetic regulation, SQAP effectively overcomes key barriers to radiotherapy efficacy.

The findings underscore the importance of integrating molecular-targeted therapies with conventional treatment modalities to address the complex nature of tumor resistance. The observed improvements in tumor control and microenvironmental modulation highlight the potential of SQAP as a valuable addition to existing therapeutic strategies.

While further research is required to validate these findings in

clinical settings, the study provides a strong foundation for the development of advanced radiosensitization approaches. Ultimately, the integration of such targeted interventions holds promise for improving outcomes in patients with aggressive and treatment-resistant cancers such as mesothelioma.

REFERENCES

1. Anderson M, Storm HH. Cancer incidence among Danish thorotrast-exposed patients. J Natl Cancer Inst 1992;84:1318–25.
2. Binder A, Serafin A, Bohm L. Abrogation of G2/M-phase block enhances the cytotoxicity of daunorubicin, melphalan and cisplatin in TP53 mutant human tumor cells. Radiat Res 2000;154:640–9.
3. Bolukbas S, Manegold C, Eberlein M et al. Survival after trimodality therapy for malignant pleural mesothelioma: radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. Lung Cancer 2011;71:75–81.
4. Folkman J, Watson K, Ingber D et al. Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature 1989;339:58–61.
5. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353–64.
6. Hanahan D, Weinberg R. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
7. Hanashima S, Mizushina Y, Yamazaki T et al. Synthesis of sulfoqionovosylacylglycerols, inhibitors of Eukaryotic DNA Polymerase α and β. Bioorg Med Chem 2001;9:367–76.
8. Harrington KJ, Billingham LJ, Brunner TB et al. NCRI clinical and translational radiotherapy research working group, guidelines for preclinical and early phase clinical assessment of novel radiosensitisers. Br J Cancer 2011;23:628–39.
9. Horsman M, Bohm L, Margison G et al. Tumor radiosensitizers-current status of development of various approaches: report of an international atomic energy agency meeting. Int J Radiat Oncol Biol Phys 2006;64:551–61.
10. Hu Y, Liu J, Huang H. Recent agents targeting HIF-1α for cancer therapy. J Cell Biochem 2013;114:498–509.
11. Iwamoto H, Nakamura T, Koga H et al. Inhibition of hypoxia-inducible factor via upregulation of von Hippel-Lindau protein induces "angiogenic switch off " in a hepatoma mouse model. Mol Ther Oncolytics 2015;2:15020.
12. Izaguirre-Carbonell J, Kawakubo H, Murata H et al. Novel anticancer agent, SQAP, binds to focal adhesion kinase and modulates its activity. Sci Rep 2015;5:15136.
13. Jain R. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005;307:58–62.
14. Karar J, Maity A. Modulating the tumor microenvironment to increase radiation responsiveness. Cancer Biol Ther 2009;8:1994–2001.
15. Kawakubo H, Kamisuki S, Suzuki K et al. SQAP, an acyl sulfoquinovosyl derivative, suppresses expression of histome deacetylase and induces cell death of cancer cells under hypoxic conditions. Bioscience, Biotechnology, and Biochemistry 2021;85:85–91.
16. Kutara K, Mochizuki Y, Ohnishi A et al. The outcome and CT findings of low-dose intensity modulated radiation therapy with SQAP in a cat with thymoma. Vet Sci 2020;7:203.
17. Marinaccio A, Binazzi A, Cauzillo G et al. Analysis of latency time and its determinants in asbestos related malignant mesothelioma cases of the Italian register. Eur J Cancer 2007;43:2722–8.
18. Mizushina Y, Watanabe I, Ohta K. Studies on inhibitors of mammalian DNA polymerase α and β: sulfolipids from a pteridophyte, Athyrium niponicum. Biochem Pharmacol 1998;55:537–41.
19. Morodomi Y, Yano T, Kinoh H et al. Bioknife, a uPA activity-dependent oncolytic sendai virus, eliminates pleural spread of malignant mesothelioma via simultaneous stimulation of uPA expression. Mol Ther 2012;20:769–77.
20. Mori Y, Sahara H, Matsumoto K et al. Downregulation of Tie2 gene by a novel antitumor sulfolipid, 3′-sulfoquinovosyl-1′-monoacylglycerol, targeting angiogenesis. Cancer Sci 2008;99:1063–70.
21. Murayama T, Takahashi K, Natori Y et al. Estimation of

future mortality from pleural malignant mesothelioma in Japan based on an age-cohort model. Am J Ind Med 2006;49:1–7.

22. Mutti L, Peikert T, Robinson B et al. Advances and New Frontiers in Mesothelioma Therapeutics. J Thorac Oncol 2018;13:1269–83.

23. Ohta K, Hanashima S, Mizushina Y et al. Studies on a novel DNA polymerase inhibitor group, synthetic sulfoquinovosylacylglycerols: inhibitory action on cell proliferation. Mutat Res 2000;467:139–52.

24. Ohta K, Mizushina Y, Hirata N. Sulfoquinovosyldiacylglycerol, KM043, a new potent inhibitor of eukaryotic DNA polymerases and HIV-reverse transcriptase type 1 from a marine red alga, Gigartina tenella. Chem Pharm Bull 1998;46:684–6.

25. Ohta K, Mori Y, Ishima M et al. Remodeling of the tumor microenvironment by combined treatment with a novel radiosensitizer, {alpha}-sulfoquinovosylmonoacylglycerol ({alpha}-SQMG) and X-irradiation. Anticancer Res 2010;30:4397–404.

26. Sahara HIM, Takahashi N. In vivo anti-tumor effect of 3′-sulphonoquinovosyl 1′-monoacylglyceride isolated from sea urchin (Strongylocentrotus intermedius) intestine. Br J Cancer 1996;75:324–32.

27. Sahara H, Hanashima S, Yamazaki T et al. Anti-tumor effect of chemically synthesized sulfolipids based on sea urchin's natural sulfoquinovosylmonoacylglycerols. Jpn J Cancer Res 2002;93:85–92.

28. Sakimoto I, Ohta K, Yamazaki T et al. Alpha-sulfoquinovosylmonoacylglycerol is a novel potent radiosensitizer targeting tumor angiogenesis. Cancer Res 2006;66:2287–95.

29. Sawada Y, Omoto K, Kohei N et al. Sulfoquinovosylacylpropanediol is a novel potent radiosensitizer in prostate cancer. Int J Urol 2015;22:590–5.

30. Sugarbaker D, Jaklitsch MT, Richards WG et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1998;117:54–65.

31. Takakusagi Y, Naz S, Takakusagi K et al. A multimodal molecular imaging study evaluates pharmacological alteration of the tumor microenvironment to improve radiation response. Cancer Res 2018;78:6828–37.

32. Tian J, Chen J, Ge C et al. Synthesis of PEGylated ferrocene nanoconjugates as the radiosensitizer of cancer cells. Bioconjug Chem 2016;27:1518–24.

33. Van T, Hanibuchi M, Kakiuchi S et al. The therapeutic efficacy of S-1 against orthotopically implanted human pleural mesothelioma cells in severe combined immunodeficient mice. Cancer Chemother Pharmacol 2011;68:497–504.

34. Verma V. Relationship and interaction of curcumin with radiation therapy. W J Clin Oncol 2016;10:275–83.

35. Weichert W, Roske A, Gekeler V et al. Histone deacetylases 1, 2 and 3 are highly expressed in prostate cancer and HDAC2 expression is associated with shorter PSA relapse time after radical prostatectomy. Br J Cancer 2008;98:604–10.

36. Weichert W, Roske A, Gekeler V et al. Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: a retrospective analysis. Lancet Oncol 2008b;9:139–48.