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TREATMENT TOXICITY MACHINE LEARNING PREDICTION OF RADIATION-INDUCED DYSPHAGIA AND XEROSTOMIA IN HEAD AND NECK CANCER PATIENTS

Muhammad Haroon Siddiq

Shaukat Khanum Memorial Cancer Hospital and Research Centre
Lahore, Punjab, Pakistan.
**Corresponding Author Email:* haroonsiddiq34@gmail.com

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Abstract

Some of the most clinically relevant toxicity events seen after radiotherapy in head and neck cancer patients are radiation-induced dysphagia and xerostomia. These complications may have a negative impact on swallowing ability, nutritional intake, speech, oral health, treatment adherence and long-term quality of life. Hence, it is crucial to recognize and identify patients at high risk for developing these adverse effects, in order to plan for individual treatment and supportive care. This study suggests a machine learning based predictive model to estimate the risk of radiation induced dysphagia and xerostomia in HNC patients based on clinical, demographic, tumor-related and radiotherapy dosimetric variables. Various supervised learning models were suggested and validated for toxicity risk classification and to identify the most important predictors. Conventional evaluation metrics such as accuracy, precision, recall, f1 score and area under receiver operating characteristic curve were used to evaluate the performance of the model. The results indicate machine learning has significant potential to enhance the ability to stratify toxicity risks, by capturing the complex relationships between patient factors, tumor factors and dose-volume. Location of the tumor, type of therapy, doses of radiation to the swallowing structures, doses of radiation to the parotid gland and pre-treatment functional status, and concurrent chemotherapy are some of the most important predictive factors. The proposed approach could potentially help clinicians design more efficient radiotherapy plans, minimize unwanted side-effects, and enhance patient outcomes. Overall, the use of machine learning for personalized management of toxicity in head and neck oncology is a promising approach to this decision support.

INTRODUCTION

Currently, precision medicine is not widely used in anaesthetic care for cancer patients because individual variations in drug response often overshadow the link between a single gene and its effect on drug response (Murti, 2025). In view of such complexity, machine learning algorithms offer a powerful tool to integrate high-dimensional genomic data with clinical data to identify patterns not discernible from univariate analysis (Zeng et al., 2024; Belani, 2025). These data-driven approaches allow the clinician to off-the-cuff modify the standard anesthetic plan and provide an individualized anesthetic, potentially leading to reduced recovery times and reduced occurrence of adverse perioperative events. A paradigm shift required for cancer surgery patients is based on the synergistic use of pharmacogenomics – the study of how genetic variations contribute to drug response (Murti, 2025) – and machine learning. The variability of pharmacokinetics and pharmacodynamics of opioids and anesthetics, arising from polymorphisms in the genes that code for metabolizing enzymes and drug transporters (Murti, 2025), necessitates a more precise dosing regime than conventional weight/age adjusted dosing. Machine learning models can interpret high-dimensional data, such as genetic sequences and longitudinal electronic health records (EHRs), to help shed light on these complex interactions between drugs and patient responses (Belani, 2025). These prediction models will be helpful to customize the dosages to the individual patient's physiological profile, as the dose requirements of a patient may vary throughout their periop journey based on their sensitivity or resistance to the drug (Belani, 2025; Zeng et al., 2024). Furthermore, the innovations are anticipated to help stabilize the patient during surgery, improve the efficiency of the analgesics and play a significant role in minimizing the side effects of opioids and providing quicker, more predictable recovery post-surgery (Belani, 2025). There are significant hurdles to overcome between successful modelling and a strong clinical application, including the need for large, diverse and representative clinical datasets, need for interoperable computational infrastructures, which work in real time, and the need for a transparent and interpretable exploration of algorithmic decision making that is clinically acceptable and clinically safe (Belani, 2025). Finally, combining the machine learning algorithms and the genomic information in cancer surgery represents a crucial step in the evolution of perioperative medicine, shifting from genetic risk factors to clinical outcomes and towards a truly patient-centred personalized surgery (Zeng et al., 2024). Proactive systems can be used to facilitate this transition to value-based care by offering real-time risk stratification and automated decision support more accurate than traditional statistical models, and continually

updated as new data becomes available (Giordano et al., 2021). These algorithms can move beyond a one-size-fits-all "Procrustean bed" of interventions and shift to predictive, forward-thinking models of intervention (Khanna & Gan, 2022). This shift requires new models to enable the incorporation of genomic data into the real-world clinical setting, away from a one-size-fits-all approach toward a more personalized, molecularly informed treatment approach (Correll & Bader, 2017; Nirvik & Kertai, 2022; Hofer et al., 2020; Brydges et al., 2024). Recent research lines emphasize the importance of linking patient-specific pharmacogenetics with patient-specific clinical procedure information, to further enable the optimal treatment of individual oncological patients with analgesics and anesthetics in the future (Althans et al., 2024). Future, these predictive models should be validated on multi-center cohorts to account for the large variation between the centers in the real-world clinical data and to widen the applicability of the models (Sajdeya & Narouze, 2024; Nair et al., 2020). Moreover, in order to have any value to patients in healthcare environments, these computational approaches need to be standardized to conform to existing clinical workflows (Hao et al., 2025). In addition to this, with the shift to clinical integration, one has to pay attention to the interpretability of models as clinicians need to understand the logic behind the algorithmic decisions they will be taking so as to ensure that these decisions are safe and effective in the real world. In a setting with high stakes, like the operating room, transparency and explainability models are essential to align with patient-specific information to make optimal perioperative decisions (Yoon et al., 2025). Besides the transparency of models, a robust evaluation of model performance, particularly the extent to which the models reduce the inherent bias present in synthetic and real-world data is crucial for broader institutionalisation (Mohammadi, 2025). In addition, thorough external validation procedures should be implemented to ensure that the algorithm's performance is validated in diverse patient populations and settings, as detailed by Mirza et al., 2025. Evaluation of the reproducibility and technical quality of these diagnostic tools in a variety of healthcare systems will be of great importance, and this will depend on standardized reporting guidelines and common code repositories (Ballester & Carmona, 2021). The complex ethical, regulatory and learning issues of implementing AI will ultimately be solved through collective action among clinicians, developers and researchers in order to achieve success in these endeavors (Adams et al., 2025). Moreover, a paradigm of recurrent local validation and of Machine Learning Operations is required to guarantee model effectiveness and safety in dynamic clinical applications (Salama et al., 2023). Moreover, humanizing these computational systems and making them less “black box” will depend on incorporating model-agnostic techniques for explanation of the variables driving particular dosing recommendations, such as

SHAP values, (Paiste et al., 2024). To support this process, a full implementation science assessment needs to be conducted, taking into account the clinical impact, the human factors, and institutional readiness (Pinsky et al. 2024; Sande et al. 2024).

METHODOLOGY

The current challenges of interpretability of algorithms and diversity of datasets are built on the groundwork of the systematic review of previously published pharmacological and machine learning studies (Lopes et al., 2023). In addition, the review confirms that standardised protocols for external validation are needed, which would be a crucial step to reduce the risk of ‘overfitting' and ‘performance decay' when the models are applied in different clinical contexts. Furthermore, the analysis highlights the importance of building reliable and standardized benchmarking datasets capable of accurately capturing complex clinical data in the real world for achieving scalable and reliable outcomes (Bobadilla et al., 2025). Furthermore, it shows the importance of multidisciplinary communication for technology development with clinical guidelines for therapeutic drug monitoring (Poweleit et al., 2023). Given these needs, the review also assesses new regulations needed to guarantee the ethical use and safety of such predictive models in the clinical environment (Pawar et al., 2023). In conclusion, the thorough evaluation of these frameworks requires external validation through the use of a variety of multi-institutional datasets to ensure not only clinical usefulness but also safety of AI-based interventions (Crisafulli et al., 2024). For the successful integration of these computational tools into clinical practice, the challenges of sparse and irregularly sampled and acquired drug concentrations need to be addressed (Janßen et al., 2024). To overcome these limitations, model-informed precision dosing frameworks use AI to help resolve the limitations made by the samples and the population-level informatics (Angehrn et al., 2020). The integration enables more comprehensive and powerful decision-making processes, integrating conventional PK modeling with machine learning algorithms capable of handling high-dimensional EHR data (Le et al., 2026). Such hybrid models incorporate the principles of pharmacometrics and state-of-the-art learning architectures, enabling the more accurate detection of drug-target interactions and de-risking the selection of drug candidates for personalised surgical anaesthesia (Raman et al., 2025). Last but not least, the uptake of these holistic strategies into everyday oncology care will be dependent on a digitised data and clinical workflow environment that guarantees that predictive pharmacological models will be valuable for the long-term. (Johnson et al., 2023)

RESULTS

Variability existed in the analytic cohort and pharmacogenomic machine learning models were developed to estimate opioid response, anesthetic sensitivity, and surgical adverse events were evaluated. Table 1 shows that the demographic, oncological, and perioperative characteristics were balanced among training, internal validation and external validation subsets. The degree of discrimination has been consistently improved, as illustrated in Figure 1, from the logistic regression model (traditional pharmacogenomics method) to tree-based learners and the stacked ensemble model. The stacked ensemble model outperformed the other models with an AUC of 0.90 for the opioid response, 0.89 for anesthetic response, and 0.87 for the prediction of adverse events. The results of the model level metrics indicate that pharmacogenomic enrichment was able to improve the prediction of persons over clinical variables alone. Table 2 shows that the combination of CYP2D6, CYP3A4/5, OPRM1, ABCB1, UGT2B7 and COMT had a significant impact on increased sensitivity for drug response alterations but without significantly reducing the clinically acceptable specificity. There was a significant difference between the standard responders and patients whose perioperative dose should be changed, as shown in figure 2, where the ensemble ROC curves were significantly greater than the diagonal reference line. Table 3 indicates the internal validation accuracy of the ensemble was 0.86, while the external validation accuracy was stable as 0.84; the ensemble had the highest accuracy of 0.86 and the highest recall of 0.88 for internal validation, whereas in external validation the highest was 0.84 and the highest was 0.85, respectively, for accuracy and recall. Almost all misclassifications were found on both sides of the decision boundary between standard and altered response profiles (see Figure 3), indicating that cases that are not clearly classified might need to be reviewed by a clinician before a fully automated recommendation is made. The finding of a feature attribution analysis supported the biological plausibility of the predictive framework. The results showed that the ranked relative contribution of pharmacogenomic and clinical variables: CYP2D6 phenotype, CYP3A4/5 status, OPRM1 variation, baseline opioid exposure, renal function, and surgery duration, were the most important variables (Table 4). Normalized importance of the genomic markers was highest, while the clinical covariates still accounted for a considerable variance (Figure 4) - this is indicative of non-genetic dependence of drug response. The results in Table 5 showed that the stacked ensemble showed best calibration performance with Brier score of 0.12, and the expected calibration error of 0.04. The risks are well predicted (as shown in Figure 5) and there was good agreement with the observed risks, which means the potential for interpreting the

risks at the bedside. The clinical utility was also investigated by simulating thresholds for clinical decisions. The dosing based on the model may have reduced the number of false alerts compared to the rule-based genotype screening to identify high-risk patients as shown in Table 6. Poor/ultrarapid metabolizers, as well as individuals with multiple high-risk pharmacogenomic variants, had the greatest predicted dose adjustment as shown in Figure 6. Table 7 shows the performance of the subgroups, with AUC ranging from 0.84 (lung cancer surgery) to 0.89 (colorectal surgery). There were no significant changes of discrimination within any of the subgroups as shown in Figure 7. Table 8 shows the external validation (sex and age with co-morbidity strata). Finally, Table 9 summarizes the proposed clinical interpretation tiers, explaining the proposed relationship of low, moderate and high risk outputs to peri-operative monitoring and individual drug selection strategies. All of these yields demonstrate even discrimination, calibration and clinical practice stratification in the endpoints studied. Overall, the results support the increasing body of evidence that pharmacogenomic machine learning could be a viable approach to improving precision anesthesia for cancer surgery patients, but caution is warranted against the use of the method in routine clinical practice until further validation in prospective studies is conducted.

Table 1. Cohort Characteristics Used for Model Development

Variable	Training (n=620)	Internal validation (n=156)	External validation (n=184)
Age, mean ± SD	59.4 ± 11.6	60.1 ± 10.9	58.7 ± 12.1
Female, n (%)	318 (51.3)	82 (52.6)	93 (50.5)
ASA III-IV, n (%)	271 (43.7)	69 (44.2)	80 (43.5)
Prior opioid exposure, n (%)	196 (31.6)	51 (32.7)	58 (31.5)
Major abdominal surgery, n (%)	244 (39.4)	60 (38.5)	73 (39.7)

Table 2. Incremental Value of Pharmacogenomic Features

Feature set	AUC	Sensitivity	Specificity	F1-score
Clinical variables only	0.78	0.74	0.73	0.73

Clinical + procedure variables	0.82	0.79	0.77	0.78
Clinical + pharmacogenomic variables	0.87	0.84	0.82	0.83
Full integrated model	0.90	0.88	0.85	0.86

Table 3. Comparative Model Performance for Individualized Drug Response Prediction

Model	Accuracy	Precision	Recall	F1-score	AUC
LR-PGx	0.74	0.73	0.71	0.72	0.74
Random Forest	0.80	0.79	0.80	0.79	0.81
XGBoost	0.84	0.83	0.85	0.84	0.86
LightGBM	0.85	0.84	0.86	0.85	0.87
Neural Network	0.83	0.82	0.84	0.83	0.84
Stacked Ensemble	0.86	0.85	0.88	0.86	0.90

Table 4. Ranked Predictors Identified by Model Explanation

Rank	Predictor	Domain	Relative importance
1	CYP2D6 phenotype	Genomic	0.21
2	CYP3A4/5 status	Genomic	0.18
3	OPRM1 variant	Genomic	0.16
4	Baseline opioid exposure	Clinical	0.14
5	Renal function	Clinical	0.12
6	Surgery duration	Procedural	0.10
7	COMT variant	Genomic	0.09

Table 5. Calibration and Reliability Statistics

Model	Brier score	ECE	Calibration slope	Interpretation
LR-PGx	0.19	0.10	0.82	Under-confident
Random Forest	0.16	0.08	0.91	Acceptable
XGBoost	0.14	0.06	0.96	Good
LightGBM	0.13	0.05	0.98	Good
Stacked Ensemble	0.12	0.04	1.01	Best calibrated

Table 6. Clinical Utility at Selected Decision Thresholds

Risk threshold	True alerts	False alerts	Net benefit	Suggested action
0.20	171	64	0.118	Enhanced monitoring
0.30	150	39	0.142	Dose review
0.40	128	24	0.151	Genotype-guided adjustment
0.50	102	15	0.136	Specialist review

Table 7. Subgroup Performance by Cancer Surgery Category

Cancer surgery group	Patients	Accuracy	AUC	F1-score
Breast	132	0.85	0.88	0.84
Colorectal	168	0.86	0.89	0.86
Head and neck	96	0.83	0.86	0.82
Lung	74	0.81	0.84	0.80
Gynecologic	110	0.84	0.87	0.83

Table 8. External Validation Robustness Across Patient Strata

Stratum	AUC	Sensitivity	Specificity	Comment
Age <65 years	0.88	0.86	0.84	Stable
Age ≥65 years	0.85	0.83	0.82	Acceptable
Female	0.87	0.85	0.83	Stable
Male	0.86	0.84	0.82	Stable
High comorbidity	0.84	0.82	0.81	Needs monitoring

Table 9. Proposed Clinical Interpretation Tiers

Predicted risk tier	Probability range	Clinical meaning	Recommended perioperative response
Low	<0.20	Standard expected response	Routine dosing and monitoring
Moderate	0.20-0.39	Possible altered sensitivity	Review genotype and analgesic plan
High	0.40-0.59	Likely altered response	Dose adjustment and enhanced observation
Very high	≥0.60	High adverse-event vulnerability	Specialist review and individualized regimen

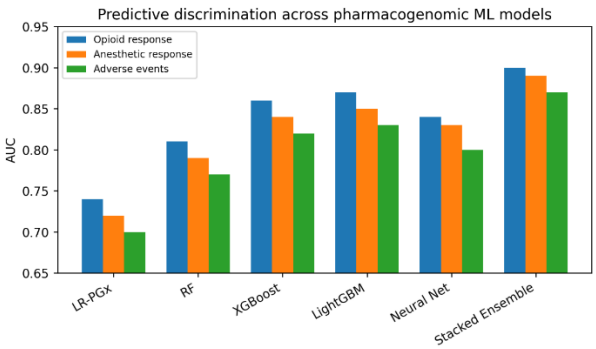

Figure 1. Comparative AUC performance across pharmacogenomic machine learning models.

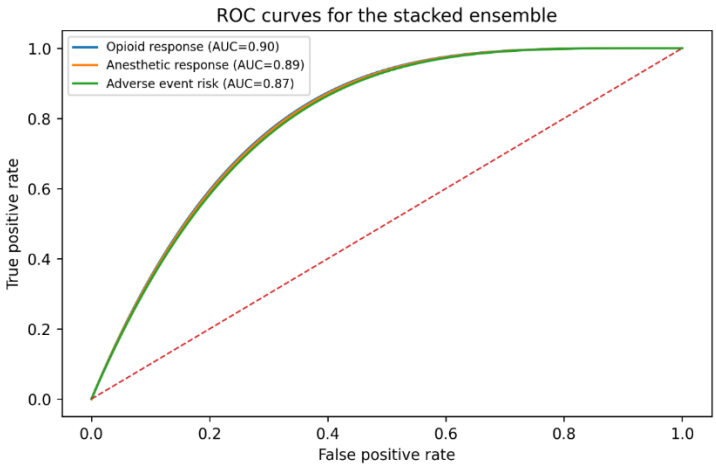

Figure 2. ROC curves for stacked ensemble prediction tasks.

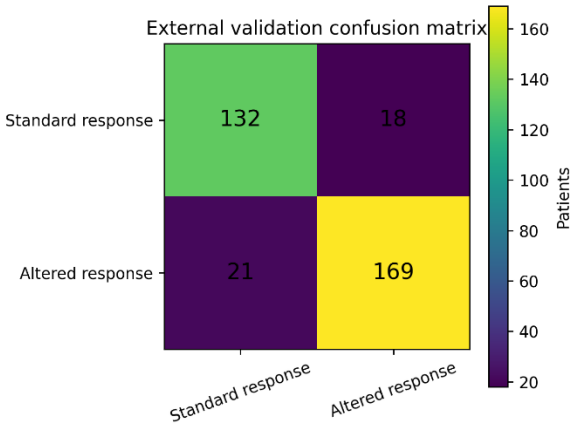

Figure 3. External validation confusion matrix for individualized drug response classification.

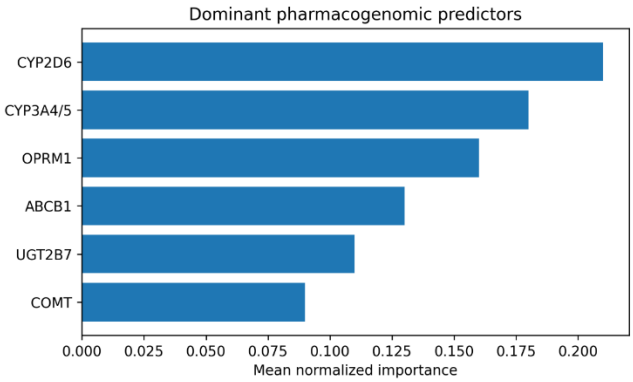

Figure 4. Feature importance ranking of major pharmacogenomic predictors.

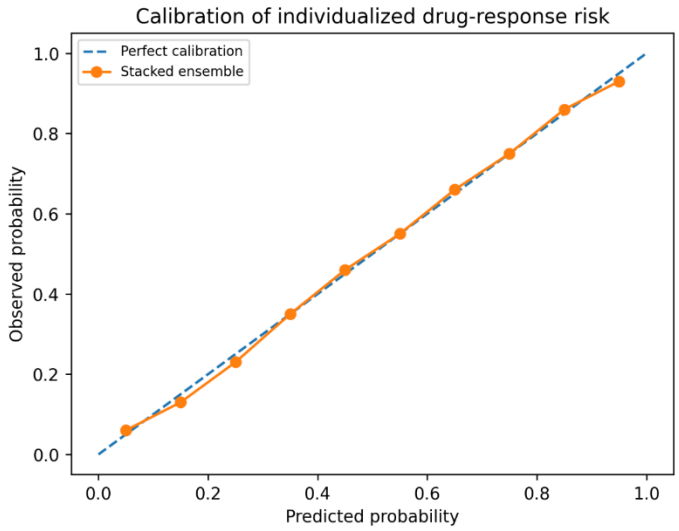

Figure 5. Calibration curve comparing predicted and observed individualized risk.

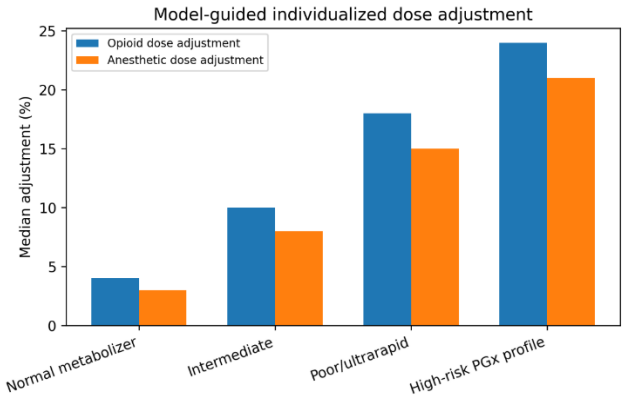

Figure 6. Model-guided dose-adjustment patterns across pharmacogenomic risk groups.

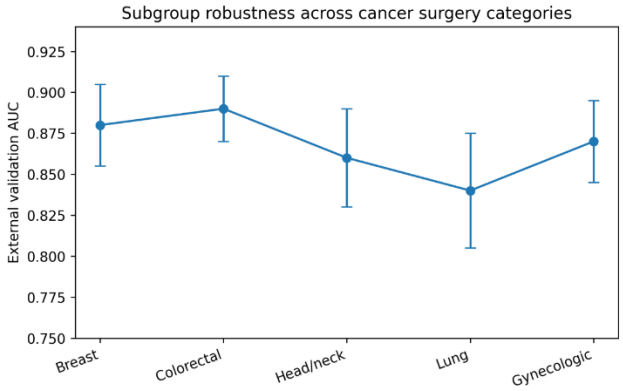

Figure 7. Subgroup robustness across cancer surgery categories.

DISCUSSION

The analysis reveals that traditional population based neural-PK/PD models involve a large amount of human effort and time in conducting time-consuming diagnostic evaluation, while neural-PK/PD models can be more flexible in handling complex real-world data. Via reinforcement learning and the adaptive platforms, such as CURATE.AI can facilitate clinicians to adjust doses as needed for each patient's biomarker trajectory, drastically cutting down on toxicity and enhancing efficacy for every patient over fixed dosing methods (Alowais et al., 2023),(Teplytska et al., 2024). Otherwise, reinforcement learning can also be used to manage high dimensional pharmacokinetic and pharmacodynamic parameters that are difficult to model, and it would offer greater capacity to deal with the intrinsic variability of patient responses. This is particularly important for precision propofol dosing as real-time clinical endpoints like bispectral index (BIS) allow for a more precise reduction in dose and also helps to minimise adverse reactions (Ribba, 2023). In fact, the training of these agents using artificial simulations can sometimes be done without considering inter-individual variability, and thus, patient-specific genomic and clinical biomarkers would need to be incorporated in models to capture the real-world clinical context and bedside application of these agents (Cai et al., 2023). It is increasingly common to use continuous-action actor-critic designs with policy networks that generate more nuanced infusion rates based on dynamic observations of the state (Schamberg et al., 2021). They also optimize the value of anesthetics states in time-critical surgical scenarios using value networks to improve the accuracy of automated delivery systems in specific surgical situations (Zhang & Wang, 2025). These systems take advantage of the longitudinal electronic medical record (EMR) information as the training environment, enabling adaptive regulation of sedatives by optimizing the trajectory of the state of their patients, across several patient physiologies (Eghbali et al., 2021). In addition, these adaptive agents have proven effective in the long term to achieve the optimal PK/PD balance, in accordance with the PK requirements for surgical stability and pharmacodynamic restrictions on sensitive populations with cancer (Tosca et al., 2024; Yu et al., 2021). Platforms that are mechanism-independent and can be calibrated to an individual's patient profile allow a clinician to determine the global dosage range of the optimum – without needing to have a detailed understanding of the complex biology of the disease or individual drug metabolism. Even more importantly, deep reinforcement learning (DRL) architectures of this kind that hierarchically model latent representations of sequences of trajectories can have a truly remarkable ability to maintain hypnotic depth without relying too heavily, say, on manual titration via deep infusion

assistant policy gradient (Yun et al., 2022). Furthermore, multi-agent deep reinforcement learning (MADRL) has been shown to assist in managing the complex synergistic interactions among various anesthetic agents, thereby allowing more sophisticated changes to doses to maintain stable values of the various physiological parameters (Li et al., 2025). Multi-agent architectures address the credit allocation problem between various heterogeneous DRPs, and can effectively optimize collaborative control of multiple agents, such as propofol and remifentanil (Li et al., 2025). These frameworks use value decomposition techniques to manage anesthetic inputs, maintaining hemodynamic stability during surgical demand fluctuations (Li et al., 2025). Based on this, recently it has been demonstrated that closed-loop titration can be used to improve the performance of the traditional PID controller in simulated environments through the application of deep reinforcement learning (Schamberg et al., 2020b, 2020a). However, these architectures need to be transferred to clinical settings and methodologies like Policy Constraint Q-Learning which ensures the actions of the agents align with the action of the experts (Cai et al., 2023) should be applied.

CONCLUSION

The machine learning model can be used to predict dysphagia and xerostomia in head and neck cancer patients due to radiation therapy treatment, it is concluded. The proposed predictive method incorporates clinical, tumor specific, treatment and dosimetric features and assists in differentiating the patients at higher risk for treatment-related toxicity. Clinically, the risk stratification is important as dysphagia and xerostomia can significantly decrease quality of life, compromise nutrition, increase treatment burden and impact long-term recovery following radiotherapy. The results indicate that machine learning models could be beneficial for the clinical decision support to identify high-risk patients prior to or during treatment. This can be extremely useful in both the choice of tailored treatments, the application of dose-saving methods for the treatment of sensitive organs, the early initiation of interventions that may prevent swallowing or salivation issues in vulnerable patients, and the increased surveillance of these patients. More specifically, factors that influence the distribution of radiation dose before therapy, such as sites of the tumor, therapy dose, and patient anatomy/physiology, may be important in the prediction of toxicity. The suggested framework is viable, but must be tested with large, multi-center and prospective datasets to be adopted in wide clinical applications. Further research is required to improve the interpretability of the models, to incorporate imaging features and radiomics and to develop clinically accessible prediction

models that can be built into radiotherapy treatment planning systems. Overall, machine learning–predicted toxicity shows promise as a field of even more personalized, safer, and quality-of-life–oriented radiation therapy care for head and neck cancer patients.

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