RADIATION ONCOLOGY—REVIEW ARTICLE

Markov models for clinical decision-making in radiation oncology: A systematic review

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Abstract

The intrinsic stochasticity of patients' response to treatment is a major consideration for clinical decision-making in radiation therapy. Markov models are powerful tools to capture this stochasticity and render effective treatment decisions. This paper provides an overview of the Markov models for clinical decision analysis in radiation oncology. A comprehensive literature search was conducted within MEDLINE using PubMed, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Only studies published from 2000 to 2023 were considered. Selected publications were summarized in two categories: (i) studies that compare two (or more) fixed treatment policies using Monte Carlo simulation and (ii) studies that seek an optimal treatment policy through Markov Decision Processes (MDPs). Relevant to the scope of this study, 61 publications were selected for detailed review. The majority of these publications (n = 56) focused on comparative analysis of two or more fixed treatment policies using Monte Carlo simulation. Classifications based on cancer site, utility measures and the type of sensitivity analysis are presented. Five publications considered MDPs with the aim of computing an optimal treatment policy; a detailed statement of the analysis and results is provided for each work. As an extension of Markov model-based simulation analysis, MDP offers a flexible framework to identify an optimal treatment policy among a possibly large set of treatment policies. However, the applications of MDPs to oncological decision-making have been understudied, and the full capacity of this framework to render complex optimal treatment decisions warrants further consideration.

Key words: clinical decisions; decision-making; Markov decision process; radiation oncology; state-transition Markov model.

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Introduction

About 50% of cancer patients receive radiation therapy (RT) at some point during their treatment.[1–3] Over the last century, RT has undergone several technological revolutions, including more recent 3D Conformal RT (3D-CRT), Intensity Modulated RT (IMRT) and Volumetric Modulated Arc Therapy (VMAT).[4,5] The advent of new technologies has led to enormous flexibility in how to deliver a prescribed radiation dose to tumours, leaving clinicians with a constellation of clinical decisions with significant effects on the outcomes of the treatment, particularly in terms of long-lasting radiation-induced injuries to the healthy tissues/organs surrounding a tumour.[6,7]

When choosing between testing and/or treatment strategies, clinicians need to evaluate the benefits and harms of each decision, commonly under the uncertainty of the corresponding outcomes, in order to make an informed decision. Decision analysis methods make this process more explicit, reproducible and evidence-based.[8,9] Decision analysis tasks underlie a broad body of knowledge, called *operations research* (OR), which borrows analytical tools from applied mathematics—including statistics, optimization and simulation—to identify optimal decisions based on evidence from the application disciplines, for example, medicine.[10,11] Over the years, OR has accompanied RT practices to answer some of their key challenges, for example, determining beam intensities and fractionation schemes.[12–14] Successful applications of *in silico* analysis and optimization theory to RT have resulted in significantly higher tumour control and overall survival rates.[15] Due to these advancements, the focus of treatment planning in certain cancer sites has now shifted from the primary aim of tumour control towards reducing the toxicity burden on the survivors (without compromising tumour control).[16–20] Markov models underlie a fundamental class of OR techniques that aim to address the uncertainty of treatment (short- and long-term) outcomes for clinical decision-making in radiation oncology.

Markov models

Consensus-based decision trees have been traditionally used to analyse uncertain outcomes of patients' response to radiation (see, e.g. refs 21–25). Despite their simplicity, decision trees become inefficient with the increased number of decisions and complexity of treatment processes. *State-transition Markov models*[26] capture the temporal trajectories of treatment outcomes through stochastic transitioning between patient's health states over time, hence offering a quantitative framework to evaluate the impact of clinical decisions on patients' health.[27,28]

In Markov models, the states represent health conditions that a patient may experience during and after the treatment. The temporal probabilistic transition from one state to another simulates the stochastic change in the patient's health status (Fig. 1). In the absence of medical interventions, these models mimic the natural progression of the disease and the patient's health evolution over time, referred to as *natural history models*.[29,30] The effect of intervention on the process is captured by allowing the transition probabilities to depend not only on the health states but also on the clinician's decisions. Given a Markov model and a treatment *policy* (a set of clinical decisions), Monte Carlo (MC) simulation can be

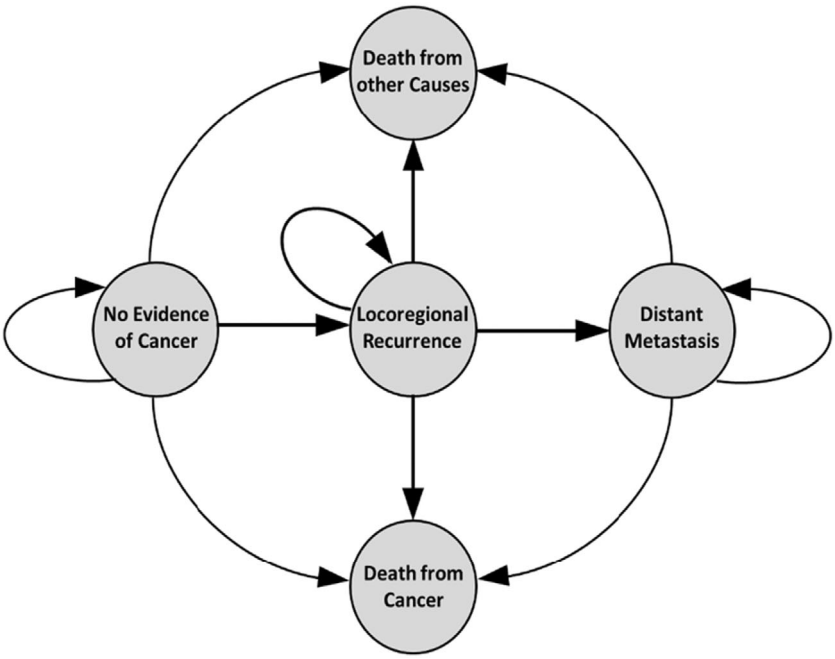

Fig. 1. A generic Markov model for the health status of cancer survivors. Arrows indicate non-zero transition probability values.

used to simulate the (probabilistic) trajectories of patients' health under the enforced policy over time, hence, to evaluate the policy based on (health utility- and cost-based) measures. Cost-effectiveness analysis is a well-known class of state-transition Markov models that (together with MC simulation) is utilized to compare two or more decision options based on the additional monetary cost incurred per unit of improvement in the outcome.

Markov decision processes

A major drawback of simulation-based analysis of Markov models is that the policies are fixed *a priori*, hence the analysis is limited to the considered policies without any guarantee that the selected policy is the best (optimal) among all the possible policies. Markov decision processes (MDPs) are developed to model the outcomes of a large number of policies (i.e. clinician's decisions) in a rigorous analytical framework and to derive an optimal set of clinician's decisions. They determine an optimal decision for each (health) state such that the expected benefit to the patient over a (finite or infinite) planning horizon is maximized. Several extensions of MDPs are also proposed, for example, *partially observable* MDPs (POMDPs),[31] which address the settings where the underlying state cannot be directly observed, a common situation in health applications. We refer to Alagoz *et al*.[32] for a comprehensive overview of MDPs.

Method

A comprehensive literature search was conducted to identify research works utilizing Markov models for clinical decision-making in RT from 2000 to 2023. The search was performed computationally through PubMed® using BioPython[33] to utilize NCBI's Entrez interface for a detailed database text search. The search strategy and review process were followed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[34] Suitable studies were identified by searching for conceptual keywords; medical subject headings (MeSH) from the National Library of Medicine were incorporated with the search strategies to ensure thorough coverage of desired search criteria. To ensure a comprehensive search, disjunctive to Markov model-related terms, 'Operations Research' [MeSH] and 'Stochastic Processes' [MeSH] were included in the search keys. The methodological keys were used in conjunction with search keys representing RT and clinical decision-making. The search terms and clauses are provided in Appendix S1.

From the initial search, restrictions were imposed using MeSH terms to exclude articles in the form of legal cases, meta-analyses, observational studies, survival analyses, retrospective studies, clinical trials and case studies. A large portion of returned studies were in the area of dose optimization, under the subject headings

'Patient Positioning' [MeSH], 'Phantoms, Imaging' [MeSH], 'Radiotherapy Planning, Computer-Assisted' [MeSH], 'Radiotherapy Setup Errors' [MeSH], 'Quality Assurance, Health Care' [MeSH], 'Quality Control' [MeSH], etc. These studies were not included in the survey due to their extensive review and coverage in the radiation oncology field.[35–39] Studies with a focus on machine learning and artificial intelligence were also not considered. Only studies with full articles available in English were used even if English abstracts were available. Five studies identified by the automatic search were survey papers with a different focus than the current work, which were excluded from the review; these are.[40–44] As a result, 135 papers were reviewed in detail, out of which 74 papers were found to be out of the scope of this survey despite including the search terms, for example, studies focusing on preventive screening protocols. A flowchart of the iterative search queries and filtering, leading to the final count of 61 articles included in this review, is provided in Figure 2.

Results

Policy comparison via Monte Carlo simulation

The Markov models introduced in the literature are dominantly used to compare two or more (fixed) policies through an MC simulation study. CEA-based studies remain the most common research works that employ Markov models in clinical decision-making in radiation therapy. Hence, the results are presented separately for the CEA- and other simulation-based studies.

Cost-effectiveness analysis

Table 1 summarizes the research studies utilizing Markov models for cost-effectiveness analysis (CEA). In addition to the policies considered and cancer sites, these works report the value of Incremental Cost-Effectiveness Ratio (ICER)and the willingness-to-pay threshold as well as the type of sensitivity analysis performed. In particular,

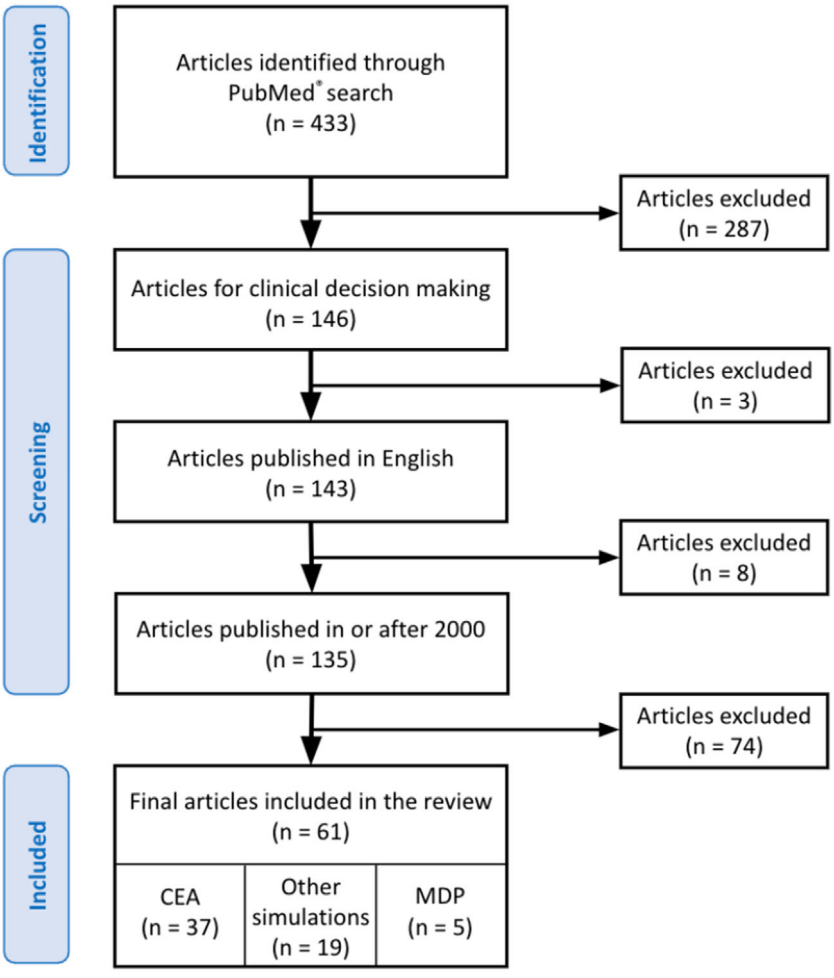

Fig. 2. Flowchart of the article search strategy and systematic review process according to PRISMA guidelines.

Table 1. Markov models for cost-effectiveness analysis

	Compares[a]	Cancer site	Simulation period (years)	ICER per QALY (threshold)	Sensitivity analysis
Carter *et al.*[46]	3D-CRT vs. IMRT	Prostate	20	$41,572 ($50,000)	One-way, Probabilistic
Vanneste *et al.*[47]	IMRT vs. IMRT + spacer for rectal structures	Prostate	5	€55,880 (€80,000)	One-way
Raldow *et al.*[48]	Five treatment policies[b]	Breast (DCIS)	10	(1 vs. 2) $1,119,81 (1 vs. 3) Policy 1 is dominant (1 vs. 4) $3,218,759 (1 vs. 5) $553,616 ($100,000)	One-way, Two-way
Peters *et al.*[49]	Focal vs. total SB	Prostate	3	Focal SB is dominant	One-way, Probabilistic
Leung *et al.*[50]	Three treatment policies[c]	Pancreas	5	(1 vs. 2) $903,915 (1 vs. 3) $71,516 ($67,392)[d]	One-way, Probabilistic
Mailhot Vega *et al.*[51]	Photon vs. proton RT	Breast	The authors consider 6 scenarios with different simulation periods; ICER is reported as a function of photon MHD for each scenario[e]		Probabilistic
Lobo *et al.*[52]	Three treatment policies[f]	Prostate	10	(1 vs. 3) $90,833 (3 vs. 2) Policy 3 is dominant ($50,000 to $100,000)	One-way, Probabilistic
Qu *et al.*[53]	Postoperative vs. Preoperative RT[g]	Soft tissue sarcoma (STS)	5	Base case: Pre-op is dominant IMRT: $1751 Lower extremity: Pre-op is dominant. ($50,000)	One-way, Probabilistic
Qu *et al.*[54]	C-PCI vs. HA-PCI	Lung (Small Cell)	8	$47,107 ($100,000)	One-way, Two-way, Probabilistic
Lundqvist *et al.*[55]	Gold Anchor GFM vs. other GFMs	Prostate	9	Gold Anchor GFM is dominant	One-way
De Bleser *et al.*[56]	Three treatment policies[h]	Prostate	5	(3 vs. 1) Policy 3 is dominant (2 vs. 3) €11,374 (€40,000)	One-way, Probabilistic
Li *et al.*[57]	IMRT vs. IMPT	Head & Neck	13	$24,135 ($33,558)[i]	Probabilistic
Lee *et al.*[58]	Pelvic CRT for all patients vs. nodal staging surgery followed by extended-field CRT	Cervix	5	$60,000	Probabilistic
Gupta *et al.*[59]	39 treatment policies[j]	Breast	Lifetime	$542–$1593	Probabilistic
Orellana *et al.*[60]	TMT vs. no TMT	Endometrial	5	$152,176–$226,559	One-way, Probabilistic
Konski *et al.*[24]	IMRT vs. 3D-CRT	Prostate	5, 10, 15	$40,101	One-way, Two-way, Probabilistic
Ng *et al.*[61]	Six treatment policies[k]	Spleen	Lifetime	$15,000–$100,000	Probabilistic
Murphy *et al.*[62]	Gemcitabine alone, Gemcitabine + CRT, Gemcitabine + IMRT, Gemcitabine + SBRT	Pancreas	5	(1 vs. 2) $126,800 (1 vs. 4) $69,500 (2 vs. 3) $1,584,100	Probabilistic
Klifto *et al.*[63]	Nine treatment policies[l]	Breast	10	−$42,109 to $23,448	Probabilistic
Van Loon *et al.*[64]	Three treatment policies[m]	Lung	5	(1 vs. 3) €69,086 (2 vs. 3) €264,033	Probabilistic
Hodges *et al.*[65]	SBRT vs. IMRT	Prostate	10	N/A	One-way, Two-way, Probabilistic
Ramaekers *et al.*[66]	IMPT vs. IMRT vs. IMPT if efficient[n]	Head & Neck	Lifetime	(1 vs. 2) €99,510 (1 vs. 3) €127,946 (2 vs. 3) €60,278	Probabilistic
EB Silveira *et al.*[67]	Three treatment policies[o]	Oesophageal	9/12	$4400	Probabilistic
Ray *et al.*[68]	Three treatment policies[p]	Liver	2	(1) $30,107 (2) $35,629 (3) $9362	One-way, Two-way
Gold *et al.*[69]	Five treatment policies[q]	Breast	15	(1 vs. 3) $367,740 (2, 4, and 5 vs. 3) dominated	One-way, Probabilistic
Edmunds *et al.*[70]	Exercise vs. Standard of care	Prostate	3	AU$50,000	One-way, Probabilistic
Li *et al.*[71]	Proton vs. Photon	Breast	Lifetime	$37,653	One-way, Probabilistic
Rodriguez-Pascual *et al.*[72]	Three treatment policies[r]	Rectal	Lifetime	(1 vs. 3) – $37,003 (2 vs. 3) –$184,115	Probabilistic
Wu *et al.*[73]	MWA vs. SBRT	Lung	5	$1,480,597	One-way, Two-way, Probabilistic
Li *et al.*[74]	Proton SBRT vs. Photon SBRT	Prostate	Lifetime	$47,457	Probabilistic
Rodriguez *et al.*[75]	Ga-DOTATATE PET/MRI vs contrast-enhanced MRI	Brain	10	$20,877	Probabilistic

Table 1. (continued)

	Compares[a]	Cancer site	Simulation period (years)	ICER per QALY (threshold)	Sensitivity analysis
Hiroshima *et al.*[76]	Proton vs. 3D-CRT	Pancreas	5	¥5,376,915	One-way, Probabilistic
Furlan *et al.*[77]	RT alone vs. Surgery + RT	Spine	Lifetime	$250,307	One-way, Probabilistic
Farah *et al.*[78]	rRP vs. rSBRT	Prostate	10	N/A	One-way, Probabilistic
Hussain *et al.*[79]	Durvalumab vs. No consolidation therapy	Lung	Lifetime	$59,850–$145,543	One-way, Two-way, Probabilistic
Ma *et al.*[80]	Total thyroidectomy vs. RAI	Thyroid	Lifetime	$2982	One-way, Two-way, Probabilistic
Yee *et al.*[81]	Piflufolastat F-18 vs. Standard of care	Prostate	Lifetime	$21,122	Probabilistic

[a]A vs. B, where B is more costly. [b]The treatment policies include (1) no testing, no RT; (2) no testing, RT only for high-grade DCIS; (3) no RT for low-grade DCIS, test for intermediate- and high-grade DCIS, RT for intermediate- or high-risk scores; (4) test all, RT for intermediate- or high-risk scores; (5) no testing, RT for all. ICERs are reported for policies 2–4 in comparison with 1. [c](3) The treatment policies include (1) gemcitabine alone; (2) gemcitabine plus intensity-modulated radiotherapy (IMRT); (3) gemcitabine plus stereotactic body radiotherapy (SBRT). ICERs are reported for policies 2–3 in comparison with 1. [d](4) The ICERs and societal willingness-to-pay threshold are converted from New Taiwan (NT) dollars to US dollars with an exchange rate of NT$1 = US $0.03333 in 2015. [e]The cohorts are identified by patients' age (40, 50, or 60 years old) as well as the presence or lack of cardiac risk factors. [f]The treatment policies include (1) 'usual care' adjuvant RT post-radical prostatectomy, (2) complete (100%) adjuvant RT post-radical prostatectomy, (3) genomic classifier (GC)-based treatment decisions post-radical prostatectomy. [g]The authors provide analysis results for three scenarios: base case, IMRT, and lower extremity. For base case and lower extremity scenarios, post-op RT proves more costly and is dominated by pre-op RT. In the case of IMRT, pre-op RT is more costly but proves cost-effective. [h]The treatment policies include (1) immediate Androgen Deprivation Therapy (ADP); (2) surveillance + delayed ADT; (3) metastasis-directed therapy + delayed ADP. [i]The ICER and societal willingness-to-pay threshold are converted from the Chinese currency RMB to US dollars with an exchange rate of US$1 = 6.47 RMB in 2021. [j]In total, 39 policies were modelled by considering the type of radiotherapy (including no radiotherapy), laterality of disease, pathologic nodal status, and dose fractionation. [k]Four of the policies are laparotomy in combination with mantle and para-aortic (MPA) radiation therapy or combined modality therapy (CMT) or chemotherapy depending on the pathological stage of the disease. The other two policies were non-surgical methods using MPA or CMT depending on the clinical stage. [l]The nine breast reconstruction methods considered were as follows: (1) direct-to-implant, (2) tissue expander-to-implant, (3) latissimus dorsi flap-to-implant, (4) latissimus dorsi, (5) pedicled transverse rectus abdominis myocutaneous (TRAM), (6) free TRAM, (7) deep inferior epigastric perforator/superficial inferior epigastric artery (DIEP/SIEA), (8) thigh-based flaps and (9) gluteal-based flaps. [m]Three imaging-based follow-up methods were considered: (1) a PET-CT scan, (2) a chest CT scan and (3) conventional follow-up with a chest X-ray. [n]If efficient, meaning for patients for which it is IMPT is expected to be cost-effective, with the rest receiving IMRT. [o]Three policies were considered as follows: (1) self-expandable stent, (2) brachytherapy and (3) Nd:YAG laser. [p]The following interventional radiology procedures were considered: (1) chemoembolization, (2) selective internal radiation therapy and (3) radiofrequency ablation. [q]Five RT policies were considered: (1) traditional whole breast RT on time, (2) balloon brachytherapy, (3) 3D-CRT, (4) traditional whole breast RT delayed by 8 weeks and (5) traditional whole breast RT delayed by 12 weeks. [r]The following three policies were considered: (1) standard resection, (2) robotic rectal resection and (3) watch and wait. 3D-CRT, 3-dimensional conformal radiation therapy; C-PCI, conventional-prophylactic cranial irradiation; DCIS, ductal carcinoma in situ; GFM, gold fiducial marker; HA-PCI, Hippocampal avoidance-prophylactic cranial irradiation; ICER, incremental cost-effectiveness ratio; IMPT, intensity-modulated proton radiation therapy; IMRT, intensity-modulated (photon) radiation therapy; MDH, mean heart dose; MWA, microwave ablation; QALY, quality adjusted life years; RAI, radioactive iodine; rRP, robotic-assisted surgery; rSBRT, robotic stereotactic body radiation therapy; RT, radiation therapy; SB, salvage brachytherapy; SBRT, stereotactic body radiation therapy; TMT, tumour molecular testing.

the following classes of sensitivity analysis were considered: (i) one-way, which investigates the sensitivity of the results to individual changes in each parameter while other parameters remain unchanged; (ii) multivariable, which quantifies the sensitivity of the results to simultaneous changes in two or more parameters (e.g. two- or three-way sensitivity analyses) and (iii) probabilistic, which measures the sensitivity of the results to simultaneous changes in *all* parameters, assuming that the value of each parameter may stochastically change within a nominal set of minimum and maximum values.[45]

Other simulation-based studies

Table 2 provides a summary of non-CEA (simulation-based) studies, which employed state-transition Markov models to compare two (or more) fixed policies solely based on health outcomes. In addition to the considered policies and cancer sites, the publications were distinguished by the utility measures employed for comparing the policies. Accordingly, Life Expectancy (LY) and Quality Adjusted Life Years (QALY) as well as their variations, such as Quality Adjusted Life Expectancy (QALE) and Quality Adjusted Life Months (QALM), were the predominant utility measures used in these studies.

Markov decision process

Among the identified articles in our literature search, only five studies use MDPs for clinical decision analysis in or involving radiation oncology; a summary of these works follows.

Gedik *et al.*[101] introduce an infinite horizon MDP to determine optimal admission policies in case of unexpected openings for proton therapy while conforming to

Table 2. Markov models for simulation-based utility comparison

	Compares	Cancer site	Utility Measure	Sensitivity Analysis
Lester-Coll *et al.*[82]	RT without HT vs. RT + 6 months of HT vs. RT + 3 years of HT	Prostate	QALE	One-way, probabilistic
Lester-Coll *et al.*[83]	SRS vs. SRS + WBRT	Brain	QALE, QALM	One-way, two-way, probabilistic
Louie *et al.*[84]	Surveillance vs. PET scan-directed SABR vs. PET scan-biopsy-SABR	Lung (non-small cell)	Prior probability threshold	Probabilistic
Kelly *et al.*[85]	No CRT vs. CRT only for leukaemic involvement vs. CRT	Brain	LE, QALY	Probabilistic
de Geus *et al.*[86]	Neoadjuvant chemoradiotherapy vs. Upfront surgery followed by chemoradiotherapy	Pancreas	LE, QALE	One-way, Two-way, Probabilistic
Lobo *et al.*[87]	Adjuvant vs. Delayed salvage RT	Prostate	QOL, Recurrence, OS, QALY	One-way, probabilistic
Sanyal *et al.*[88]	The authors consider different treatment policies for patients based on the level of risk at the time of diagnosis†	Prostate	Lifetime direct costs, QALY	Probabilistic
Wallis *et al.*[89]	Adjuvant vs. Salvage RT	Prostate	QALE, LE	Probabilistic
Austin, *et al.*[90]	Proton vs. X-ray RT	Brain (SBC)	QALY	N/A
Rinkel *et al.*[91]	Neurosurgical vs. Radiosurgical vs. Conservative management	Brain (CCM)	QALY, Risk of 5-year recurrence	Probabilistic
de Buck van Overstraeten *et al.*[92]	Nonoperative management vs. Radical resection following neoadjuvant chemoradiotherapy	Rectum	LY, QALY	One-way, Two-way
Nair, *et al.*[93]	The authors develop multiple models and consider seven post-RT surveillance policies for each model.‡	Head & Neck	Recurrence detection time	N/A
Morrison *et al.*[94]	(1) Initial observation followed by microsurgical resection if the tumour grows, (2) Initial observation followed by gamma knife if the tumour grows, (3) Primary microsurgical resection, (4) Primary radiosurgery via gamma knife	Brain	QALY	Two-way
Sher *et al.*[95]	PBI vs. WBRT	Breast	QALE	One-way, Two-way, Three-way
Louie *et al.*[96]	SBRT vs Surgery	Lung	QALE, OS	One-way, Three-way
McInerney *et al.*[97]	1) Observation / natural history, 2) Microsurgery, 3) Stereotactic radiosurgery	Brain	QALY	Probabilistic
Wang *et al.*[98]	RT following breast-conserving surgery vs. No RT under different margin scenarios (free, close, or positive margin)	Breast	QALY	One-way, Probabilistic
Alibhai *et al.*[99]	Radical prostatectomy vs. External beam RT vs. Watchful waiting	Prostate	QALE	Probabilistic
Shimizu *et al.*[100]	Localized vs. Biochemical failure after curative therapy	Prostate	QALE	N/A

†The treatment policies for low-risk patients include Active Surveillance (AS), Radical Prostatectomy (RP), Brachytherapy (BT) and Intensity-Modulated Radiation Therapy (IMRT). The treatment policies for patients at intermediate risk include RP, IMRT, IMRT + BT and IMRT + Androgen Deprivation Therapy (ADT). The treatment policies for high-risk patients include RP, IMRT + ADT, and IMRT + ADT + BT. ‡The models differ based on HPV status (positive or negative) and the stage of the disease (III, IVA, or IVB). Each policy is composed of a PET scan at month 3 (after the treatment) followed by a series (of 0–6) CT scans at fixed intervals. Abbreviations: CCM, cerebral cavernous malformations; CRT, cranial radiation therapy; HT, hormonal therapy; IMRT, intensity modulated radiation therapy; LE, life expectancy; LY, life years; OS, overall survival; PBI, partial breast irradiation; QALE, quality adjusted life expectancy; QALM, quality adjusted life month; QALY, quality adjusted life year; QOL, quality of life; RT, radiation therapy; SABR, stereotactic ablative radiotherapy; SBC, skull base chordoma; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiation surgery; WBRT, whole breast radiation therapy; WBRT, whole-brain radiation therapy.

the patient mix and capacity restrictions. To avoid the computational complexity of large-scale instances, the authors propose an 'aggregate' MDP with a tractable action space to approximate optimal patient admission policies. Their numerical results show that the aggregate MDP provides acceptable approximations for the original MDP optimal policies.

Gocgun[102] develops a finite horizon MDP to find an optimal RT scheduling policy under the uncertainty of patients' arrival. The author considers a centre serving different types of cancers with various treatment times, urgency levels and capacity requirements; due to the huge number of states and actions for realistic instances, they present an *approximate dynamic programming* method to solve the problem. The reported numerical results suggest that the approximate optimal policy outperforms a 'myopic' policy.

Ng *et al.*[103] propose a POMDP to identify optimal imaging policies for head and neck cancer (HNC) patients who

receive definitive radiotherapy; they use finite and infinite horizon POMDPs to obtain short-term and long-term optimal policies, respectively. The authors use the simulation of a surveillance program to examine the effectiveness of the policies generated by POMDP. Their results suggest adequate information on the relapse status of HNC patients can be obtained with less frequent scan policies.

Maass and Kim[104] develop a finite horizon MDP to optimize multi-modality cancer management, that is, to identify an optimal sequence of treatment modalities based on a patient's data in multimodal cancer therapy. To see if the optimal policies given by MDP coincide with the clinical intuition, numerical simulations are performed with simplified patient states and clinically intuitive utility functions. They report promising results for potential applications of the proposed MDP in treatment decision-making.

Finally, Imani *et al*.[105] propose two finite horizon MDPs to determine optimal intervention and treatment strategies for *in situ* breast cancer when the decision is optimized (i) to achieve the highest QALY, and (ii) to incur the least treatment costs. The authors consider an action space including wait (do-nothing decision), prophylactic mastectomy, radiation therapy, chemotherapy, and the combinations of these modalities, across all health states. The study demonstrates lower treatment costs for mastectomy and chemotherapy compared to other alternatives. Interestingly, the wait decision leads to the highest accrued QALY compared to any other intervention.

These publications collectively demonstrate the applicability of MDPs in oncological decision-making. Yet, there exists a vast pool of oncological decision-making problems that can be tackled by MDPs and their extensions.

Discussion

Since their first applications to medical decision-making in the early 1980s, Markov models have been extensively employed to model patients' recurrent health states and their underlying uncertain transitions. As a result, Markov models have proved to be a rigorous tool to study the effects of a *fixed* series of actions (i.e. a policy) on the patient's health status evolution over time, particularly for medical decision-making in radiation oncology. However, the number of works investigating an optimal treatment policy (in the presence of a large number of possible policies) remains limited in radiation oncology literature.

As an extension of Markov models, the Markov decision process (MDP) is a powerful tool to analyse stochastic processes under the control of a decision maker. When the treatment process involves sequential (clinical) decisions at different times, and there are several options available for each decision, the number of possible treatment policies grows quite rapidly. In this case, a comprehensive simulation-based analysis would require comparing all these policies with each other, suggesting a computationally intractable analysis process. MDPs alleviate the computational burden. Despite recent efforts to equip radiation oncology with high-performance computing resources,[106] the computational efficiency of analytical models remains crucial to wide adaptability of the radiation oncology practice to informatics tools.

MDPs are particularly suitable for a broad class of radiation oncology decision-making problems, which regard the following question: 'when is the optimal timing to perform a diagnostic test (e.g., imaging), or intervene the planned treatment considering the harms and benefits?' The complicating factor when answering this question is the inherent uncertainty in the response of the tumour and/or organs at risk (OARs) to the treatment. Following the MDP framework, the underlying states may be presented, for example, using clinical indicators (e.g. accumulated dose) or image-based biomarkers (such as those explored for head-and-neck cancers (HNC)[107,108]), and probabilistic transitions between possible states may be inferred from randomized clinical trials (RCTs), or even institution-level datasets. By incorporating the costs (harms) or rewards (benefits) of available clinical actions, an MDP model can analytically compute the optimal timing of interventions.

An emergent application of optimal-timing problem arises in Magnetic Resonance (MR)-Guided Adaptive Radiation Therapy (ART) planning.[109,110] The primary goal of ART is to perform (possibly frequent) adaptations in the treatment plan as a function of the tumour's and OARs' responses to the radiation; MR-Guided ART is a novel implementation of ART, which seeks revising the original treatment plan based on daily on-treatment MRIs. While practical resource limitations prohibit daily replanning, clinical studies further demonstrate that the benefit of highly frequent replanning may not improve treatment outcomes homogeneously among all patients[111]; hence, the optimal timing of adaptations remains an open question. In this setting, MDPs can be developed to capture the stochasticity of the outcome of adaptations and to compute an optimal policy (i.e. a series of adaptation decisions), for example, to minimize the toxicity burden to the patient by the end of the treatment.

Relevant to radiation oncology, MDPs can also aid in making decisions that help maintain the patient's overall health during treatment, thus increasing the success chance of RT. As an example, pain management remains a key component of certain cancer patients receiving radiation therapy, for example, HNC patients who often require highly fractionated treatments. While the physician aims at prescribing certain drugs for pain alleviation in HNC patients, the side effects of such drugs (e.g. sleepiness,

drowsiness, drug dependence, etc.) may interfere with the healthy nutrition, a critical factor for continuing the RT treatment. Considering the large number of possible combinations of pain alleviation drugs, an MDP-based model may be developed to compute an optimal combination of the drugs as well as their dosages, for example, to minimize the treatment interruptions due to poor nutrition.

Extensions of MDPs can also be made to a broad range of clinical decision-making scenarios in cancer care. Examples are optimal timing of surgery following neoadjuvant interventions and optimal surveillance programs for cancer survivors for early detection of recurrent and/or secondary malignancies. Further, MDPs can be combined with advanced computational biological modelling to bring the utility of MDPs to new frontiers. Examples are the inclusion of recent developments in genetic oncologic testing within MDPs to find the optimal triaging of patients based on their probability of first-line failure for cost and unnecessary toxicity reduction. It is for this reason, and the paucity of MDP results from our literature review, that bring attention to the unmet utilization of this tool for clinical decision-making in the field of oncology.

While MDPs offer a high degree of flexibility in modelling clinical decisions with uncertain outcomes, their implementation has its own challenges. Similar to any other modelling framework, the fidelity of a such model highly depends on the inputs utilized for model calibration. In particular, the inference of the state transition probabilities and the values (e.g. rewards) associated with each health state can be challenging. Compared to simulation-based studies, MDPs require richer data sets as the probabilistic outcomes must be evaluated for each possible action. This, in part, may explain the paucity of MDP models in radiation oncology in addition to the higher complexity of MDPs. Ideally, the transition probabilities and state values can be inferred from randomized control trials (RCTs). In the absence of RCTs, the model parameters are often inferred from the relevant literature or institutional data sets. Sensitivity analysis can always be utilized to infer the robustness of the model to the estimated transition probabilities and/or reward values.

Markov decision processes and their extensions have proved successful outside of the oncological space both for medical decision-making (e.g. screening[112] and organ transplantation[113]) and other applications.[114] This promotes a new area of informatics development in radiation oncology and presents a practical and rigorous analytical framework to render complex oncological decisions, which are out of the reach of the existing tools. Collaborative efforts, particularly those involving interdisciplinary expertise from oncologists and operations research scientists remain the key to develop such evidence-based decision-support tools. Developing visualized metrics may also facilitate an intuitive understanding of the models, hence promoting the use of complex decision-support tools in the clinic. Specifically, tailored funding opportunities by NIH will attract interdisciplinary collaborative works to address crucial oncological decision-making problems and stimulate breakthrough improvements in cancer treatment outcomes.

Conclusion

A comprehensive PubMed® literature search was conducted to identify research studies employing Markov models for clinical decision-making in radiation oncology, published from 2000 to 2023. As a result, 61 research articles were reviewed, and their findings were summarized in two main categories: (i) studies that aim to compare two (or more) fixed treatment policies based on Monte Carlo simulation results and (ii) studies that seek an optimal treatment policy through Markov decision process (MDP) analysis. Among the reviewed works, 56 papers fall in the first category, which was further subdivided into cost-effectiveness analysis (CEA) and studies focusing on utility comparison only. While all these works rely on Monte Carlo simulation results to provide a direct comparison between the considered (fixed) treatment policies, CEA studies prove to be popular among simulation-based models. For the second category (i.e. MDP analysis), five studies were identified and reviewed. The MDP framework can be considered an extension of the simulation-based methods in the presence of a large number of complex policies to identify an optimal policy. It is discussed that MDP provides a more comprehensive setting (than simulation-based studies) for clinical decision analysis, which, based on the survey results, is yet to be fully explored. Examples of novel applications of MDP analysis for clinical decision-making are provided, stimulating further research in this area.

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Ethical statement

As a literature study, this work did not require any approval from the institutional review board. The study did not include any human participants or animal experimentation.

Data availability statement

In the Appendix S1, the authors will share the query based on which the literature survey was conducted.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Search terms and structure.