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OPERATIONS RESEARCH TECHNIQUES in CANCER TREATMENT

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Operations research, also known as management science, can be defined as the discipline of applying advanced analytical methods to help make better decisions. It successfully enhances the decision processes of cancer treatment. This study aims to give an idea about state-of-the-art and a brief description of the combination of operations research techniques and cancer therapies. Although there is recently an increase of researches in this synergistic area, there is still a blank to be discovered. The outcomes of this interdisciplinary approach may be utilized by cancer clinicians.

Key Words: Radiotherapy, Chemotherapy, Cancer therapy, Optimization, Interdisciplinary studies, Medical operations research.

KANSER TEDAVİSİNDE YÖNEYLEM ARAŞTIRMASI TEKNİKLERİ

Yönetim bilimi olarak da bilinen yöneylem araştırması, daha iyi kararlar vermek amacıyla ileri analitik yöntemlerin uygulanması disiplini olarak tanımlanabilir. Yöneylem araştırması kanser tedavilerindeki karar süreçlerini de başarılı bir şekilde desteklemektedir. Bu çalışma, söz konusu çerçevede, mevcut durum hakkında bir fikir vermeyi ve kanser tedavileri ile yöneylem araştırmasının bileşimini kısaca tanımlamayı amaçlamaktadır. Bu sinerjik alanda son zamanlarda artan sayıda araştırmalar olmasına karşın, yine de keşfedilmeyi bekleyen bir boşluk olduğu söylenebilir. Bu disiplinler arası yaklaşımın çıktıları kanser klinisyenlerince kullanılabilir.

Anahtar Sözcükler: Radyoterapi, Kemoterapi, Kanser terapisi, Optimizasyon, Disiplinlerarası çalışmalar, Medikal yöneylem araştırması.

INTRODUCTION

Cancer has been one of the most common health concerns over the last decades. A number of therapies have been developed and so many researchers, from different disciplines, have been studying in both theoretical and clinical views on the issue. Although cancer therapy is heavily standing on the shoulders of the profession of medicine, it may benefit from a wide range of disciplines such as physics, mathematics and operations research.

In a nutshell, operations research (OR), also known as management science, can be defined as the discipline of applying advanced analytical methods to help make better decisions [INFORMS, 06/26/2006]. It may also be taken into consideration as the science of better or the science of decision making. From its origin in World War II to date, OR has been used in a wide range of areas from military operations, economics, urban planning, sports, forestry to agriculture and communications, to health care in both managerial and clinical means.

OR can be determined as an intersection of optimization, statistics and computer science. In this manner, the three elements of medical operations research, which creates a link to medicine, may be interacted with medical areas in the following way: statistics corresponds to biostatistics, computer science to bioinformatics when optimization to medical optimization [Esen, Çetin and Tolun Esen, 2006].

OR highly supports the process of medical, especially clinical, decision making that this study emphasizes. The current literature of this effort has been generally specified in cancer aspect, efficiently in diagnosis and treatment procedures.

This paper focuses on the OR methods, which offers optimal and efficient rather than spontaneous decisions, used in cancer treatments composed of mainly radiation and chemo therapies due to the fact that the current literature is concentrated on these types. While giving an introductory to clinical operations research in cancer, a basic approach in radiotherapy is discussed in detail to extend the mind.

1. RADIATION THERAPY

The problem of designing an optimal radiation density profile in the patient is often referred to as the *fluence map optimization* (FMO) problem [Romeijn, Ahuja, Dempsey, et al., 2006, pp. 201-216]. In other words, the use of OR facilitates optimal treatment plannings that the damage of cancerous cells are maximized when that of normal tissues are minimized. Most of the studies in radiotherapy are dealing with this problem. Even though there are a lot of commercial IMRT softwares, which all use local search or heuristic approaches [Romeijn, Ahuja, Dempsey, et al., 2006, pp. 201-216] of OR, the main effort is to develop exact methods to find a satisfactory treatment plan. Most employed techniques of OR on the subject are linear programming, nonlinear programming, quadratic programming, integer programming, multicriteria optimization, Monte Carlo simulation, Markov analysis and also appropriate hybrit approaches. For instance, Romeijn et. al. [2006, pp. 201-216] have recently developed a linear programming model for FMO. Fymat et. al. [1998, pp. 117-146] developed a nonlinear minimization search method for optimizing the radiotherapy treatment plan. Redpath et. al. [1975, pp. 158-164] applied quadratic programming techniques to the optimization of radiation field weighting in radiotherapy planning. For external beam radiotherapy, a linear-quadratic model of radiobiological effect is established by Dale et. al. [2005, pp. 47-51].

Some researchers have developed optimization models over integers. Lee et. al. [2003, pp. 165-181] applied integer programming to IMRT planning. Also, Lee et. al. [2000, pp. 995-1004] employed mixed integer programming technique for optimization of radiosurgery treatment planning. A large-scale optimization procedure of beam weights is developed by Langer et. al. [1990, pp. 887-893].

Another OR approach is multicriteria optimization technique. As an instance, Hamacher et. al. [2002, pp. 145-61] determined the issue in a multiobjective view. Also, Yu [1997, pp. 1445-1454] studied multi-objective decision theory in radiation therapy.

A number of researchers used simulation, which is a common tool especially used for dosimetry in radiotherapy planning. A few from the literature are as follows. Shahine et. al. [2001, p. 404] used a Monte Carlo dose calculation for an inverse-planning algorithm. Sgouros [2005, p. 18S] used Monte Carlo simulation to calculate the observed fraction from source-target organ pair. Dewaraja et. al. [2005, pp. 840-847] used clinically realistic voxel-phantom simulations in the evaluation of activity quantification and dosimetry.

Markov analysis is one of the remarkable probabilistic OR techniques. It is employed especially for cost-effectiveness analysis in radiation therapy. In breast cancer treatment, Lundkvist et. al. [2005, pp. 179-185] used Markov analysis for economic evaluation of proton radiation therapy. There are also other applications of this manner such as Konski, Watkins-Bruner, Brereton, et al. [2006, pp. 51-57] and Konski, Watkins-Bruner [2004, pp. 513-519].

The other important topic in radiotherapy is to handle organ motion. Some varieties of OR techniques appear in the literature. Monte Carlo simulation [Paganetti, Jiang, Adams, et al., 2004, pp. 942-950], multistage optimization [Lee, Cha, Bortfeld, et al., 2005] and Markov analysis [Çetin, 2006] are remarkable ones. Van Herk [2004, pp. 52-64] presented a review paper of errors and margins in radiotherapy. In addition, Seminers in Radiation Oncology holds one special issue for the topic [Bortfeld and Chen, 2004, p. 1].

As an organized source, based on OR applications to radiation therapy, a workshop has been made by National Cancer Institute-National Science Foundation of USA [2002].

An Illustrative Example

An illustrative OR application, multiobjective optimization technique, to radiotherapy is given below from [Matthias, 2005]. Radiation dose distribution in the body depends on intensity of radiation beams in a linear fashion. Let $x \in R^n$ be a vector describing an intensity map, where n is the total number of sub-beams. The patient body is discretized into m dose points according to magnetic resonance imaging (MRI) or computed tomography (CT) scans. The dose delivered to the dose points is then Ax, where A is a mxn matrix. Supposing that we have l critical structures, we can partition the rows of A according to the set of dose points in the tumor T in a critical structure $S_i, i = 1,2,\ldots,l$ or in healthy tissue N and form submatrices A_T, A_{S_i}, A_N respectively. Let l_T denote the prescribed tumoricidal dose, u_T be an upper bound on the dose in the tumor, u_{S_i} be upper bounds on the dose in critical structure i, and u_N be an upper bound on the dose in healthy tissue. It is assumed that these bounds apply to every dose point in the tumor, critical structure, and healthy tissue, respectively.

Ideally, we would like to design a treatment that delivers a uniform dose of l_T to the tumor and no dose at all to critical structures and healty tissue. Since this is usually physically impossible we have to accept some underdosing z_T in the tumor or overdosing $z_{C_i}, i = 1,2,\ldots,l$ and z_N in critical structures and healthy tissue. Naturally, the values of $z_T, z_{S_1},\ldots, z_{C_l}$ should be kept as small as possible.

Therefore, the problem can be described via the following multiobjective optimization problem, where e is a vector of ones of appropriate dimension.

$$\begin{aligned}
\min \quad & z_T, z_{S_1},\ldots, z_{S_l}, z_N \\
\text{subject to} \quad & A_T x + z_T e \geq l_T \\
& A_T x \leq u_T \\
& A_{S_i} x - z_{S_i} e \leq u_{S_i}, \quad i = 1,2,\ldots,l \\
& A_N x - z_N e \leq u_N \\
& z_{S_i} \geq -u_{S_i}, \quad i = 1,2,\ldots,l \\
& z_N \geq 0 \\
& x \geq 0.
\end{aligned}$$

In this model, the goal is to find efficient solutions $(x, z) \in R^{n+l+2}$ such that the maximal underdosing of any tumor dose point and the maximal overdosing of any critical structure and any healthy tissue dose point is simultaneously minimized.

2. CHEMOTHERAPY

The synthesis of chemotherapy and OR methodology is also wellcome. Eli Lilly & Company efficiently implemented multivariate methods and multiple logistic regression to identify and neutralize the toxic side effects for drug ALIMTA, which is a new antifolate class of cancer drug [INFORMS, 06/26/2006]. There are also core OR techniques stimulated chemotherapy. At the top of the rank simulation takes place (eg, see Liang, Leung and Mok, [2006, pp. 237-245] and Chui, Cai, Wang, et al. [2006, pp. 99-101.]). In analytical view, Markov analysis is a leading one among stochastic techniques for chemotherapy, for such a recent example see [Qi, 2006, pp. 187-195]. Although in the case of chemotherapy the literature is not as rich as in radiotherapy, there are different methods employed other than foregoing techniques. To give an idea, for example, integer programming [Puterman, Schumacher and Sandor, 1990, pp. 273-286] and also cost-effectiveness analyses are made via OR related methods (eg, Exposito, Hernandez, Feijoo, et al. [2003, pp. 895-902]).

3. OTHER THERAPIES and the SCOPE

As known, some combination therapies are implemented for cancer treatment such as chemoradiotherapy and immunochemoradiotherapy as well as some supplementary therapies such as immunotherapy, photodynamic therapy (photoradiation therapy, phototherapy, or photochemotherapy), gene therapy and antiangiogenesis therapy [American Cancer Society, 06/29/2006]. The literature on these therapies in conjunction with OR is virtually silent, but it is a fact that such therapies have a high potential to cooperate with OR algorithms. As an example; Esen, Çetin and Tolun Esen [2006] developed a multiobjective immunochemoradiotherapy dose planning model. Also, OR related adjuvant therapies are implemented. For an instance, Karnon and Brown [1998, pp. 133-140] used decision tree, Markov analysis and simulation to take the economic evaluation of adjuvant therapies for breast cancer.

It should be mentioned that there are successful OR applications to cancer diagnosis such as optimal biopsy protocols for prostate cancer [Sofer, Zeng and Mun, 2003, pp. 63-74] even though the main emphasis is on the treatment phase in this study. Sofer and Zeng [2002, pp. 45-61] developed a transformation method to solve easily integer nonlinear optimization problem in Sofer, Zeng and Mun [2003, pp. 63-74] for optimal biopsy strategies.

There are also published books and journals that include OR related applications to medicine, paying a special attention to cancer research. Operations Research and Health Care [Brandeau, Sainfort and Pierskalla, 2004], offering a comprehensive review literature, contains a range variety of models. Also, Cancer Modeling and Simulation [Preziosi, 2003] focuses on mathematical view and simulation. From mathematical aspects of biology, Murray [2003] offers some therapeutic models of cancer. Moreover, Annals of Operations Research [2003] published a special issue on optimization in medicine.

DISCUSSION and CONCLUDING REMARKS

This effort comprises a classification of OR techniques applied to cancer treatment. Radiation therapy outweighs chemotherapy and other treatments in benefiting from OR techniques. In this descriptive study, it is also given an illustrative radiotherapy model to reveal the efficiency of the approach.

It is observed that some combination and additional therapies other than radiotherapy and chemotherapy may also be encouraged to cooperate with OR. In addition, it may be claimed that there is an increasing attention to this interdisciplinary area that is why the studies on this topic are recently arising.

As showing the motivation on the synergistic area, this informal structure tends to institutionalize to establish a new platform. A remarkable example of this trend is Center for Operations Research in Medicine of Georgia Institute of Technology, which mostly focuses on cancer research, founded in 1998 [Center for Operations Research in Medicine, 06/29/2006]. In this context, cancer clinicians may use the advantages of this initiated synergy made up of OR and medicine.

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