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医学放射物理

Model Analytics辅助的智能放疗计划建模

王美娇[1,2],李莎[2,3],岳海振[2],弓健[2],项小羽[2],郭文[1],张艺宝[2]
1.中国疾病预防控制中心辐射防护与核安全医学所,北京 100088;2.北京大学肿瘤医院暨北京市肿瘤防治研究所放疗科/恶性肿瘤发病机制及转化研究教育部重点实验室,北京 100142;3.北京大学医学部医学影像物理实验室,北京 100191

【摘 要】**目的:**利用瓦里安公司开发的Model Analytics(MA)工具减少人工处理RapidPlan模型离群值的繁琐和主观因素导致模型构成的不确定性,评估MA工具在效率、改善统计学参数及模型优化效果等方面的表现。**方法:**①选取81例优质计划导入RapidPlan系统并建立初始模型;②将初始模型上传MA进行自动分析统计,根据报告提示对离群值进行批量统计学确认,比较模型验证前后统计学指标的变化;③利用20例测试病例评估统计学确认前后RapidPlan模型的剂量学表现,并与原临床计划比较。**结果:**MA只需几分钟便可得到构成模型计划的几何学、剂量学等特征统计,5轮分析共找出8个股骨头剂量学离群值,分别高于各自预测范围上限的11.11%、5.88%、5.56%、5.56%、5.00%、5.26%、5.56%和5.88%,R^2由0.32提高至0.45;仅用一轮分析便找出所有3个膀胱几何和剂量学离群值,其中几何离群值分别高于均值62.22%或低于均值55.35%,剂量学离群值高于预测范围上限3.33%,处理完离群值后,R^2由0.35升至0.37。测试计划表明,RapidPlan计划质量显著优于人工计划(P<0.05),使用验证前后的模型可分别降低股骨头剂量23.15%和27.55%,降低膀胱剂量8.14%和6.79%。**结论:**使用MA工具可快速获取模型构成计划的整体描述,并准确查找出模型中的离群值,从而提高智能放疗计划建模的效率,但统计学确认对模型的剂量学表现影响不大。

【关键词】智能计划;RapidPlan;Model Analytics;机器学习;建模
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Modeling for knowledge-based plan assisted with Model Analytics

WANG Meijiao[1,2], LI Sha[2,3], YUE Haizhen[2], GONG Jian[2], XIANG Xiaoyu[2], GUO Wen[1], ZHANG Yibao[2]
1. National Institute for Radiological Protection, Chinese Center for Disease Control and Prevention, Beijing 100088, China; 2. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Radiotherapy, Peking University Cancer Hospital & Institute, Beijing 100142, China; 3. Medical Imaging Physics Laboratory, Health Science Center, Peking University, Beijing 100191, China

Abstract: Objective To reduce the component uncertainty induced by the complexity and subjectivity of outlier processing during the RapidPlan model verification with the use of Varian Model Analytics (MA), and to evaluate the efficiency, statistical and dosimetric performances of MA. **Methods** An initial RapidPlan model was configured with 81 best-effort plans. The established initial model was uploaded to the MA for automated statistical analysis, and MA suggested that outliers were processed batch by batch. Statistical indexes were compared before and after verification. The dosimetric outcomes of 20 validation cases were re-planned by the RapidPlan models before and after verification, and compared with the clinical manual plans. **Results** MA took a few minutes to analyze the geometric and dosimetric statistics of the plans. Eight dosimetric outliers were reported in 5 rounds of verifications, which were higher than the estimated upper limits by 11.11%, 5.88%, 5.56%, 5.56%, 5.00%, 5.26%, 5.56% and 5.88%, respectively. R^2 value was improved from 0.32 to 0.45 after statistical verification. Only performing 1 round of verification, we found out all 3 outliers for urinary bladder, where the values of geometric outliers were 62.22% higher or 55.35% lower than the majority average values. The value of dosimetric outlier was 3.33% higher than the estimated upper limit. The R^2 value was improved to 0.37 from 0.35 after statistical verification. Validation cases suggested that RapidPlan plan prevails over conventional manual plan significantly (P<0.05), in which the dose to femoral head was reduced by 23.15% and 27.55% using model before and after verification, respectively, and the dose to urinary bladder was reduced by 8.14% and 6.79%, respectively. **Conclusion** Statistical features of RapidPlan plans can be acquired quickly using MA which detects outliers hence

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【作者简介】王美娇,硕士研究生,研究方向:放射医学,E-mail: 18301663962@163.com
【通信作者】张艺宝,博士,高级工程师,硕士生导师,研究方向:医学物理,E-mail: ybzhang66@163.com

enhances the efficiency of model configuration for knowledge-based planning. The effect of statistical verification on the dosimetric outcome is marginal.

Keywords: knowledge-based plan; RapidPlan; Model Analytics; machine learning; modeling

前 言

从2012年Appenzoller等[1]和Yuan等[2]团队各自将机器学习技术应用于放疗计划设计，到瓦里安近期上市的商用系统RapidPlan，基于人工智能的放疗计划已经在效率[3]、质量(包括头颈[4]、肺[5]、食管[6]、乳腺[7]、肝[8]、前列腺[9]、宫颈[10]、直肠[11-12]等病种)、一致性[13-14]等众多方面展示出优于人工设计的特点。甚至有学者预言十年内自动计划将取代传统人工设计[15]。基于历史数据建立和调试剂量体积直方图(DVH)预测模型是实现智能计划的关键过程，虽然RapidPlan可以生成各种复杂的统计学参数和图表，但依靠设计者本人的统计学知识判断处置离群值和强影响点(以下统称离群值)以改进模型不仅费时费力，而且文献报道的方法和效果也莫衷一是[10, 16-17]。

为减少人工处理离群值的繁琐和主观因素导致模型构成的不确定性，瓦里安公司最近开发了基于web的Model Analytics(MA)工具，并免费供给RapidPlan用户试用。作为常规临床前测试和质控，本工作系统评估了MA工具在运行效率、改善统计学参数及模型优化效果等方面的表现。

1 材料与方法

1.1 RapidPlan模型的建立

北京大学肿瘤医院直肠癌术前同步推量SIB VMAT模型的建立方法、统计确认及验证结果详见早前报道[11-12,17-19]，现简要总结如下：81例历史计划经高年资物理师逐一精修后被导入RapidPlan系统，其中处方剂量、解剖结构、布野方式、剂量分布等关键数据被自动提取并拟合成DVH预测模型。所有计划均采用单个整弧、10 MV光子、5°准直器角度，在配置Millenium 120 MLC的加速器上实现95%计划肿瘤靶区(PGTV)及计划靶区(PTV)分别大于等于50.6和41.8 Gy的处方剂量，分22次完成。人工统计学确认过程包括逐个检查所对应计划的几何离群值(Z-scores)大于3.5、剂量学离群值(Studentized Residual, SR)大于3、强影响点数据(Cook's Distance, CD)大于4。其中，Z-scores、SR和CD值分别反映离群值与样本均值的差异、残差与预测标准差之商，以及从模型中去除某病例后对其他病例残差的影响。参照瓦里安说明书及文献[10, 16]报道方法，对每个危及器官模型中的可疑离群值进行分批处理(每次1~2个)，及时评估统计学参数并验证计划以确认模型优化效果。

1.2 MA辅助的模型改进和统计学确认

将未经人工统计学确认的初始模型及其包含的原始计划信息以DICOM格式从Eclipse计划系统中导出(所有计划均依照HIPPA做匿名处理)，并一键上传服务器，由MA自动批量统计用于建模的原始计划数据的几何学特征、剂量学特征，并对初步拟合的DVH预测模型进行分析，评估回归模型参数的可决系数(R^2)、Z-scores、SR和CD。参考报告的建议检查各离群值并进行批量处理。由于每次处理完离群值后均需要重新拟合新的模型，从而可能产生新的离群值，因此需要将重新拟合后的模型重复上述步骤，直至不再提示新的离群值且各项统计学指标均变好。

1.3 模型验证和剂量学参数比较

另选20例同类型的临床测试计划，验证比较统计学确认前后RapidPlan模型的优化效果，并与临床计划比较。所有计划按处方剂量归一(95%体积满足100%处方剂量)，计算比较如下剂量学参数：① PGTV及PTV的均匀性指数(HI_{PGTV}和HI_{PTV})，$HI=(D_{2\%}-D_{98\%})/D_{50\%}$；② PGTV与PTV的适形指数($CI_{PGTV}$和$CI_{PTV}$)，$CI=V_{100\%}/V_{target}$；③ 股骨头及膀胱的平均剂量。

1.4 统计学方法

用SPSS 21.0软件提供的Shapiro-Wilk方法检验数据分布正态性，符合正态分布采用配对t检验，不符合正态分布则采用非参数检验，$P<0.05$为统计学有显著意义。

2 结 果

2.1 模型构成计划整体特征描述

模型数据库中，所有股骨头平均剂量的均值±标准差为(16.70±2.19) Gy，最大最小值分别为20.90和11.20 Gy。总体积的均值±标准差为(200.60±53.92) cm^3，最大最小值分别为334.91和95.82 cm^3。射野内体积的均值±标准差为(200.60±53.92) cm^3(100.00%±0.00%)，最大最小值分别表示为334.91 cm^3(100.00%)和95.82 cm^3(99.98%)。与目标靶区重叠体积的均值±标准差分别表示为(0.05±0.01) cm^3，最大值为0.05 cm^3(0.02%)，最小值为0。MA找出所有8个股骨头离群值一共经历了5轮分析，表1列举了每轮报告的剂量学离

表1 5轮分析报告的股骨头剂量学离群值(MA未报告几何离群值)

Tab.1 Dosimetric outliers of femoral heads reported in 5 rounds of analysis (no geometric outlier was reported by Model Analytics)

Round (#of outliers)	D_{mean}/Gy		Actual	*t*/s
	Estimated range	Actual		
First Round (2)	14	18	20	95
	12	17	18	
Second Round (2)	13	18	19	125
	14	18	19	
Third Round (2)	16	20	21	200
	15	19	20	
Fourth Round (1)	14	18	19	180
Fifth Round (1)	13	17	18	155

All outliers were ascribed to the actual mean dose outside the estimated range.

群值及其原因(MA未报告几何离群值)。

所有膀胱平均剂量的均值±标准差为(25.10±2.96) Gy,最大最小值分别为34.53和18.57 Gy。总体积的均值±标准差为(283.90±169.77) cm^3,最大最小值分别为744.34和55.19 cm^3。射野内体积的均值±标准差为(245.40±148.84) cm^3(86.23%±7.53%),最大最小值分别为633.14 cm^3(99.79%)和40.35 cm^3(60.99%)。与目标靶区重叠体积的均值±标准差分别表示为(38.50±29.22) cm^3(13.77%±7.53%),最大最小值分别为161.44 cm^3(39.01%)和0.29 cm^3(0.21%)。只用一轮MA分析就找出了所有3个不同原因的膀胱离群值(耗时95 s),分别为:几何离群值1的射野内体积38.50%显著低于均值86.23%;几何离群值2与靶区的重合体积161.44 cm^3显著高于均值60.99 cm^3;剂量学离群值1的平均剂量30 Gy显著高于预测范围24~29 Gy。

2.2 剂量学比较和统计学确认

表2展示20例测试计划分别使用验证前后RapidPlan模型的优化结果与原临床计划之间的比较。

表2 验证前后RapidPlan模型优化结果与原临床计划之间的比较(20例测试计划结果)

Tab.2 Dosimetric comparison of 20 clinical plans and their re-optimized results using RapidPlan models before and after verification

		HI		CI		D_{mean}/Gy	
		PGTV	PTV	PGTV	PTV	Femoral head	Urinary bladder
Clinical	Mean	0.06	0.27	1.03	1.02	14.95	24.74
	SD	0.01	0.08	0.03	0.03	1.59	4.54
Before	Mean	0.05	0.26	1.07	1.05	11.13	22.72
	SD	0.00	0.01	0.06	0.02	1.47	3.49
After	Mean	0.05	0.26	1.07	1.06	10.83	23.06
	SD	0.00	0.01	0.06	0.02	1.69	3.45
*P*1 value		0.00*	0.03*	0.02	0.00	0.00*	0.06^
*P*2 value		0.00*	0.03*	0.00	0.00	0.00*	0.06^
*P*3 value		0.68*	0.69*	0.43	0.37	0.03*	0.06^

* Paired *t* test; ^ Friedman test, otherwise Wilcoxon test. *P*1: Clinical *vs*. Before; *P*2: Clinical *vs*. After; *P*3: Before *vs*. After; HI: Homogeneity index; CI: Conformity index; PGTV: Planning gross tumor volume; PTV: Planning target volume

3 讨 论

MA工具可多次上传模型文件,发现各危及器官中的离群值并提出处理建议。运行效率方面,MA工具仅需一键上传服务器,几分钟即可统计出建模原始计划的几何学特征、剂量学特征等,可自动提取出危及器官的最大、最小、平均剂量和标准差。MA工

具可一次挑选出多个危及器官的离群值，即可发现结构误配等明显错误，也可报告明显偏离主要数据的点。上传所需时间与网速快慢有关。相比之下，人工方法挑选离群值时，主观性强，缺少标准，费时费力，一次只能处理极少数量的离群值[17]。

由表1可知，第一轮两个剂量学离群值的实际平均剂量分别高于预测范围上限的11.11%和5.88%，第二轮高出5.56%和5.56%，第三轮高出5.00%和5.26%，第四轮和第五轮分别高出5.56%和5.88%。离群值数目逐轮减少，且股骨头回归模型的R^2变好，由0.32变成0.45。

膀胱剂量学离群值的实际平均剂量高于预测范围上限3.33%，几何学离群值的射野内体积低于均值55.35%，另一几何学离群值与目标靶区重叠体积高于均值62.22%。统计学确认后膀胱的R^2变好，由0.35变成0.37。

表2展示的模型优化效果中，RapidPlan计划显著优于人工优化的临床计划(P<0.05)，与早先报道一致[17-18]，具体表现在：靶区剂量更均匀、更适形(主要与模型中的靶区优化参数设置有关)，危及器官受量降低(与RapidPlan生成的个体化优化参数和新的PO算法有关[20])。其中，模型验证前后股骨头平均剂量与临床计划平均剂量相比，分别降低23.15%和27.55%，膀胱平均剂量与临床计划平均剂量相比，分别降低8.14%和6.79%。RapidPlan模型验证前后，除股骨头剂量变化有统计学意义外，其他差别不大，且无统计学意义。这些结果也与早前基于人工的模型确认结果一致[16]。

4 结 论

使用MA工具可快速获取模型构成计划的整体特征描述，并准确查找出模型中的离群值，从而提高智能放疗计划建模的效率，但统计学确认对模型的剂量学表现影响不大。

【参考文献】

[1] APPENZOLLER L M, MICHALSKI J M, THORSTAD W L, et al. Predicting dose-volume histograms for organs-at-risk in IMRT planning[J]. Med Phys, 2012, 39(12): 7446-7461.

[2] YUAN L, GE Y, LEE W R, et al. Quantitative analysis of the factors which affect the interpatient organ-at-risk dose sparing variation in IMRT plans[J]. Med Phys, 2012, 39(11): 6868-6878.

[3] CHANG A T, HUNG A W, CHEUNG F W, et al. Comparison of planning quality and efficiency between conventional and knowledge-based algorithms in nasopharyngeal cancer patients using intensity modulated radiation therapy[J]. Int J Radiat Oncol Biol Phys, 2016, 95(3): 981-990.

[4] TOL J P, DELANEY A R, DAHELE M, et al. Evaluation of a knowledge-based planning solution for head and neck cancer[J]. Int J Radiat Oncol Biol Phys, 2015, 91(3): 612-620.

[5] FOGLIATA A, BELOSI F, CLIVIO A, et al. On the pre-clinical validation of a commercial model-based optimisation engine: application to volumetric modulated arc therapy for patients with lung or prostate cancer[J]. Radiother Oncol, 2014, 113(3): 385-391.

[6] FOGLIATA A, NICOLINI G, CLIVIO A, et al. A broad scope knowledge based model for optimization of VMAT in esophageal cancer: validation and assessment of plan quality among different treatment centers[J]. Radiat Oncol, 2015, 10(1): 1.

[7] FOGLIATA A, NICOLINI G, BOURGIER C, et al. Performance of a knowledge-based model for optimization of volumetric modulated arc therapy plans for single and bilateral breast irradiation[J]. PLoS One, 2015, 10(12): e0145137.

[8] FOGLIATA A, WANG P M, BELOSI F, et al. Assessment of a model based optimization engine for volumetric modulated arc therapy for patients with advanced hepatocellular cancer[J]. Radiat Oncol, 2014, 9(1): 236.

[9] NWANKWO O, MEKDASH H, KUNCORO D S, et al. Knowledge-based radiation therapy (KBRT) treatment planning *versus* planning by experts: validation of a KBRT algorithm for prostate cancer treatment planning[J]. Radiat Oncol, 2015, 10(1): 111.

[10] HUSSEIN M, SOUTH C P, BARRY M A, et al. Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy[J]. Radiother Oncol, 2016, 120(3): 473.

[11] WU H, JIANG F, YUE H Z, et al. Applying a RapidPlan model trained on a technique and orientation to another: a feasibility and dosimetric evaluation[J]. Radiat Oncol, 2016, 11(1): 108.

[12] WU H, JIANG F, YUE H Z, et al. A dosimetric evaluation of knowledge-based VMAT planning with simultaneous integrated boosting for rectal cancer patients[J]. J Appl Clin Med Phys, 2016, 17(6): 78-85.

[13] GOOD D, LO J, LEE W R, et al. A knowledge-based approach to improving and homogenizing intensity modulated radiation therapy planning quality among treatment centers: an example application to prostate cancer planning[J]. Int J Radiat Oncol Biol Phys, 2013, 87(1): 176-181.

[14] BERRY S L, MA R, BOCZKWSKI A, et al. Evaluating inter-campus plan consistency using a knowledge based planning model [J]. Radiother Oncol, 2016, 120(2): 349-355.

[15] SHARPE M B, MOORE K L, ORTON C G. Within the next ten years treatment planning will become fully automated without the need for human intervention[J]. Med Phys, 2014, 41(12): 120601.

[16] DELANEY A R, TOL J P, DAHELE M, et al. Effect of dosimetric outliers on the performance of a commercial knowledge-based planning solution[J]. Int J Radiat Oncol Biol Phys, 2016, 94(3): 469-477.

[17] 吴昊, 蒋璠, 岳海振, 等. 瓦里安RapidPlan模型训练中统计离群值的处理及其剂量学影响[J]. 中国医学物理学杂志, 2016, 33(7): 649-653.
WU H, JIANG F, YUE H Z, et al. Statistical outlier processing and dosimetric effect in Varian RapidPlan model verification[J]. Chinese Journal of Medical Physics, 2016, 33(7): 649-653.

[18] 蒋璠, 张艺宝, 岳海振, 等. 基于经验的放疗计划模型训练及其初步应用[J]. 中华放射肿瘤学杂志, 2016, 25(11): 1223-1227.
JIANG F, ZHANG Y B, YUE H Z, et al. The model training of knowledge-based radiotherapy treatment planning and its preliminary application[J]. Chinese Journal of Radiation Oncology, 2016, 25(11): 1223-1227.

[19] 吴昊, 刘杰, 岳海振, 等. 基于Web的剂量体积直方图数据自动提取工具开发及验证[J]. 中国医学物理学杂志, 2016, 33(5): 433-436.
WU H, LIU J, YUE H Z, et al. Development and validation of Web-based automated dose-volume histogram data analyzer[J]. Chinese Journal of Medical Physics, 2016, 33(5): 433-436.

[20] JIANG F, WU H, YUE H Z, et al. Photon optimizer (PO) prevails over progressive resolution optimizer (PRO) for VMAT planning with or without knowledge-based solution[J]. J Appl Clin Med Phys, 2017, 18(2): 9.

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