Cancer Management and Research

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ORIGINAL RESEARCH

Comparative Study of Auto Plan and Manual Plan for Nasopharyngeal Carcinoma Intensity-Modulated Radiation Therapy

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose and Objective: Auto planning might reduce the manual time required for the optimization and could also potentially improve the overall plan quality. The aim of this study is to demonstrate the statistical comparison of automatic (AU) and manually (MA) generated nasopharyngeal carcinoma (NPC) intensity-modulated radiation therapy (IMRT) plans.

Materials and Methods: The study included 105 nasopharyngeal carcinoma patients, admitted to our hospital. The patients underwent IMRT treatments. The clinically delivered plans were performed with Eclipse (Version 11.0) using manual optimization. The same plans were optimized successively in Pinnacle^{TM3} (version 9.10) treatment planning system using the auto plan software package module. D95 (dose of 95% volume) and D98 (dose of 98% volume) were calculated for the targets and maximum dose (Dmax) and mean dose (Dmean) for the organ at risks (OARs); moreover, the average doses of each target and OARs for 105 patients were evaluated.

Results: There is no significant difference in the homogeneity of the target between AU and MA treatment plans, while a significant difference is observed for what is concerning the OARs or most of OARs in 105 patients, OAR doses were significantly reduced in AU plan. For OARs which have no significant difference between AU and MA plans are highlighted, the mean dose of OARs in AU plans was at least not higher than MA plans.

Conclusion: Nasopharyngeal carcinoma IMRT plans made by an automatic planning tool met the clinical requirements for target prescription dose; moreover, the dose of normal tissues was lower than in MA plans. Clinical physicists' time can be saved and the influence of factors such as the lack of experience in treatment planning can be avoided.

Keywords: auto planning, manual planning, nasopharyngeal carcinoma

Introduction

Head and neck cancer is one of the most common malignant tumors all over the world. Because of the high sensitivity to radiotherapy and chemotherapy, radiotherapy with concurrent chemotherapy has become the main method of treatment of nasopharyngeal carcinoma, and especially with the introduction of IMRT,[1] patients at early stages have achieved higher disease-free survival rate. Because of the complex anatomy of the head and neck, most tumor targets are very irregular, and IMRT has been shown to improve the quality of life for patients undergoing therapy by sparing the critical organs surrounding the tumor. Therefore, head and neck cancer has become the biggest beneficiary of this new technology.[2–4] At present, IMRT technology is widely used in the treatment of head

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DovePress
http://doi.org/10.2147/CMAR.S226495

and neck tumors, and studies have confirmed that IMRT can improve the target dose and achieve an ideal therapeutic effect.[5–8] But treatment plans for head and neck cancer are highly complex due to multiple dose prescription levels and numerous OARs close to the target;[9] each OAR has its own limiting dose, so the quality of treatment plan depends greatly on the skill and experience of clinical physicists, and clinical physicists need to spend plenty of time in order to make a high-quality treatment plan. As a result, IMRT planning can be a time-consuming and frustrating task, and the quality of treatment plans with similar target dose prescriptions and normal tissue constraints will vary greatly between physicists and institutions.[10] The automated system's treatment plan can effectively reduce manual time and also reduce the difference between treatment plans designed by physicists through trial-and-error. It has been shown that it is possible to almost fully automate or accelerate this functionality where plans are created much faster and with greater consistency and quality.[11] The research of auto-IMRT plans can be divided into two parts: one is to develop system algorithms to automatically generate and optimize model parameters, and the other is using the target parameters required for the new program which were extracted from a large number of treated patient planning database to optimize for new treatment plan. This research used mdaccAutoPlan system as a plug-in to the Pinnacle^3 treatment planning system (TPS), this system uses system algorithms and an iterative approach to optimize model parameters. It can set beam angle, planning structures, and objective function parameters automatically without human intervention. In terms of tumor coverage and normal tissue sparing, the computer-generated plans are intended to be better than, or at least equivalent to, those designed by physicists through trial-and-error. It is also our goal that the methodology is executable rapidly enough to be used in routine. Currently, automatic planning has been used in cervical cancer,[12] and radiofrequency ablation planning of liver cancer[13] and prostate cancer,[14] and studies have shown that automatic planning achieves better results than manual planning. In this paper, we used the mdaccAutoPlan system to generate 105 IMRT autoplans of head and neck cancer, and then compared the dose distribution with IMRT manual plans, to explore the advantages of IMRT autoplans for head and neck cancer.

Materials and Methods

Patient Characteristics

From August 2015 to August 2018, 105 patients treated for nasopharyngeal carcinoma in our hospital were selected; the patients and their characteristics are reported in Table 1.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethical committees of Sichuan Cancer Hospital and all patients provided written informed consent, in accordance with the Declaration of Helsinki and our editorial ethics policy.

Planning Target Volume (PTV) Contouring and Prescription

All PTV was contoured by experienced physicians in our hospital in accordance with "The common view and guideline of expert on target area and dose design for intensity-modulated radiation therapy for nasopharyngeal carcinoma 2010".[15] Planning gross tumor volume (PGTV), PGTVn was constructed from GTV, GTVn (bilateral neck nodes gross target volume) with the addition of a 3 mm margin, with the description dose from 68 Gy to 70 Gy, PCTV66 was constructed from clinical target volume (CTV) with the addition of a 3mm margin, with the description dose of

Table 1 Patient Characteristics

	Number	%		Number	%
Pathology type			Clinical stages		
Undifferentiated type of keratinizing carcinoma	15	14	T		
Undifferentiated type of non-keratinizing carcinoma	90	86	1	6	6
Sex			2	36	34
Male	75	72	3	41	39
Female	30	28	4	22	20
Age			N		
≥60	29	28	1	19	18
<60	76	72	2	75	71
GTV (gross target volume)			3	11	11
≤100cc	37	35	M		
100~200cc	60	57	0	105	100
>200cc	8	8	1	0	0

66 Gy, for PCTV56 and PCTVn, the description dose was 56 Gy. The goal of our center is to reach at least 95% of the prescription dose of every PTV.

OARs Dose Limiting

The recommended plan assessment requirements for OAR followed in our center are shown in Table 2.

Plan Design

Manual Plan Design

For this study, 105 nasopharyngeal carcinoma treatment plans were selected, and all these cases were generated on the Eclipse treatment planning system (version A11.0). The treatment plans of all patients were generated by experienced medical physicists in our center and all the manual plans were optimized according to our standard clinical practice. All the basic parameters and beam angles of 105 patients were the same, the seven treatment beams were oriented at the angles of 153°, 102°, 51°, 0°, 309°, 258°, 207°, and all beams were delivered at 6 MV according to our center's standard.

Auto Plan Design

MdaccAutoPlan software provides a template with configurable parameters. Regions of interest (ROIs) (e.g. PTV or expanded cord), placement of points of interest (POIs), prescriptions, beam geometries, optimization options, and prioritized optimization goals can be defined automatically; the only inputs to the system were the delineations of planning target and organs at risk.

All of the 105 treatment plans were replanned by the mdaccAutoPlan system available in Pinnacle3 (version 9.10). In order to reduce the influence on the final dose distribution, in this study, we used the same position of isocenter and same beam angles as the manual plan.

Table 2 Dose Limit of OARs

OAR	Max Dose	Limiting Dose
Brain stem Spinal cord Optic nerve Optic chiasm Temporal lobe Lens	54 Gy 45 Gy 50 Gy 50 Gy 60 Gy 25 Gy	>60 Gy≤1% >50 Gy≤1% 55 Gy 55 Gy >65 Gy≤1%
	Mean dose	
Pituitary	≤50 Gy	
Parotid gland	Double sides<25 Gy when PTV was complicated (PTV overlap with parotid) as low as possible	
Oral cavity Cochlea	≤40 Gy ≤45 Gy	

Data Statistics

All AU and MA plans were delivered to Matlab software. D_2, D_{50}, D_{95}, D_{98} of PGTV, PCTV60, PCTV56, and PCTVn were calculated in Matlab, and their homogeneity index (HI), HI= $(D_2 - D_{95})/D_{50}$ and conformal index (CI)[17] of PGTV and PCTV56+PCTVn were calculated, where CI= $(V_{ptv}/V_{ptv,ref}) \times (V_{ref}/V_{ptv,ref})$, Vptv, ref is the volume of the target area wrapped around the reference isodose line, Vptv is the target volume, and Vref is the total volume wrapped around the reference isodose line. The reference dose in this paper is the prescribed dose, so the higher the CI value, the worse the prescription dose conformal. We chose OARs of the brain stem, spinal cord, lens, temporal lobe, optic nerve, and optic chiasm to calculate their Dmax, and oropharynx, parotid, mandible joint, pituitary, thyroid, and cochlea to calculate their Dmean. Then, we recorded the monitor unit (MU) of the auto plan and the manual plan of every patient, and performed the *t* test of the parameters above, where $P<0.05$ means the difference was significant.

Results

Target Dose Comparison

In terms of target coverage, CI, HI, and MU of 105 patients, there is no significant difference between AU and MA plans; the D_{95}, CI, and HI of AU and MA plans are shown in Tables 3 and 4 respectively. The monitor units of MA and AU plans are 1754.6±117.2 and 1774.4±87.8, respectively; $P=0.074$.

OAR Dose Comparison

Organs are divided into serial organs (brain stem, spinal cord, crystal, optic nerve, etc.) and parallel organs (parotid gland, oropharynx, mandible joint, etc.) in accordance with their radiation biological characteristics. The average value of serial organs maximum doses in 105 patients are shown in Table 5, and the average numbers of parallel organ doses are shown in Table 6. From Tables 5 and 6, we can see that all the

Table 3 Comparison of D95 of MA and AU Plan (X± χ)

Target	MA D_{95} (cGy)	AU D_{95} (cGy)	*P*
PGTV	6722.4±223.8	6823.4±188.7	0.2
PGTVn	6834.4±253.7	6756.2±208.4	0.3
PCTV60	6067.4±464.4	5992.2±452.2	0.3
PCTV56+PCTVn	5623.7±593.4	5605.6±528.1	0.3

Table 4 Comparison of CI and HI for AU and MA Plan (X± χ)

HI	MA Plan	AU Plan	*P*
PGTV+PGTVn	0.0684±0.005	0.0832±0.007	0.11
PCTV60	0.0986±0.006	0.1542±0.006	0.86
PCTV56	0.1838±0.015	0.1856±0.018	0.69
PCTVn	0.2296±0.021	0.2688±0.024	0.06
CI			
PGTV+PGTVn	1.35±0.21	1.34±0.15	0.92
PCTVn	1.54±0.27	1.57±0.28	0.14

Table 5 Comparison of Max Dose for Serial Organs (cGy, X± χ)

OARs	MA Plan	AU Plan	*P*
Brain stem	4922.3±452.7	4868.1±342.6	0.7
Spinal cord*	3870.1±297.3	2506.3±734.4	0.0
Left lens*	478.3±159.0	409.9±90.0	0.0
Right lens*	472.5±164.1	423.3±109.7	0.0
Left temporal lobe	6328.0±450.3	6327.0±429.8	0.7
Right temporal lobe	6458.8±431.4	6422.8±431.4	0.3
Left optic nerve*	2412.3±1661.7	2100.0±1503.1	0.0
Right optic nerve*	2578.6±1865.4	2071.1±1667.7	0.002
Optic chiasm	2389.3±1692.2	2331.3±1696.2	0.42

Note: *Indicates a statistically significant difference in maximum dose ($P<0.05$).

Table 6 Comparison of Mean Dose for Parallel Organs (cGy, X± χ)

OARs	MA Plan	AU Plan	*P*
Oropharynx	3328.9±313.4	3126.5±313.0	*P*=0.001
Left parotid gland*	2859.2±313.2	2322.3±506.0	*P*=0.0
Right parotid gland*	2845.6±334.6	2452.5±431.9	*P*=0.0
Left mandible*	3913.4±432.2	3105.0±470.4	*P*=0.0
Right mandible*	3884.0±401.9	3087.6±407.2	*P*=0.0
Left mandible joint*	3661.1±631.4	1794.6±709.4	*P*=0.0
Right mandible joint*	3631.5±709.2	1767.4±824.3	*P*=0.0
Pituitary	2818.7±1283.2	2643.9±1500.9	*P*=0.158
Thyroid*	2143.5±561.9	1667.5±332.7	*P*=0.0
Left cochlea*	3953.2±468.9	3468.3±807.1	*P*=0.0
Right cochlea*	4032.3±493.7	3513.5±752.6	*P*=0.0
Normal tissue* (NT)	932.1±110.2	814.1±79.9	*P*=0.025

Note: *Indicates a statistically significant difference in mean dose ($P<0.05$).

doses of OARs in AU plans are significantly lower than in MA plans, except for brain stem, optic chiasm, temporal lobe, and pituitary.

Comparison of Dose-Volume Histogram (DVH)

Below are three average DVHs of the parotid gland, mandible joint and spinal cord in the 105 planned cases (Figure 1) which are representative of the comparison of dose distribution obtained in AU and MA plans.

Comparison of Dose Distribution

Figure 2 shows a comparison of isodose lines from a typical patient of AU and MA plans which intercepts a representative level of the same layer. It can be seen that the AU plan was visually more conforming and had better OAR sparing and steeper dose fall away from the targets.

Comparison of MA Plans in Pinnacle TPS and Eclipse TPS

In our research, AU plans were generated in Pinnacle TPS and MA plans were generated in Eclipse TPS, in order to observe if there is a significant difference between two systems in planning optimization; 20 patients were randomly selected from the 105 cases to do MA plans in Pinnacle TPS. The dose comparisons are as given in Tables 7–9.

Discussion

This study showed that there is no significant difference in target dose between AU and MA plans, but the AU plan has clear advantages in protecting OARs as well as saving labor time, as also concluded by Ilma Xhaferllari et al,[18] Hazell et al[19] and He et al.[20] From the comparison of AU and MA plans, we can see that the AU plan has an important protective effect on the brain stem, spinal cord, temporal lobe, parotid gland, and other organs. For example, it can theoretically reduce radiation damage for the brainstem and spinal cord, the incidence of cognitive impairment may be reduced and it reduces the incidence of xerostomia and the chance of oral infection.

In this study, all patients of the AU plan were independently implemented with the mdaccAutoPlan automated planning software and met clinical requirements without any human intervention, which greatly reduces the working time. In the majority of radiotherapy institutions in China, the quality of radiotherapy planning is limited because of the large number of patients and limited planning time of the clinical physicists, but the automatic planning system not only can make it easier for radiotherapy institutions to make quality plans in limited resources, but also can give physicists more time to focus on quality assurance, rather than spending time in program optimization. If there are other clinical requirements, it can be directly adjusted and optimized further on the original plan. Therefore, AU planning can be treated as

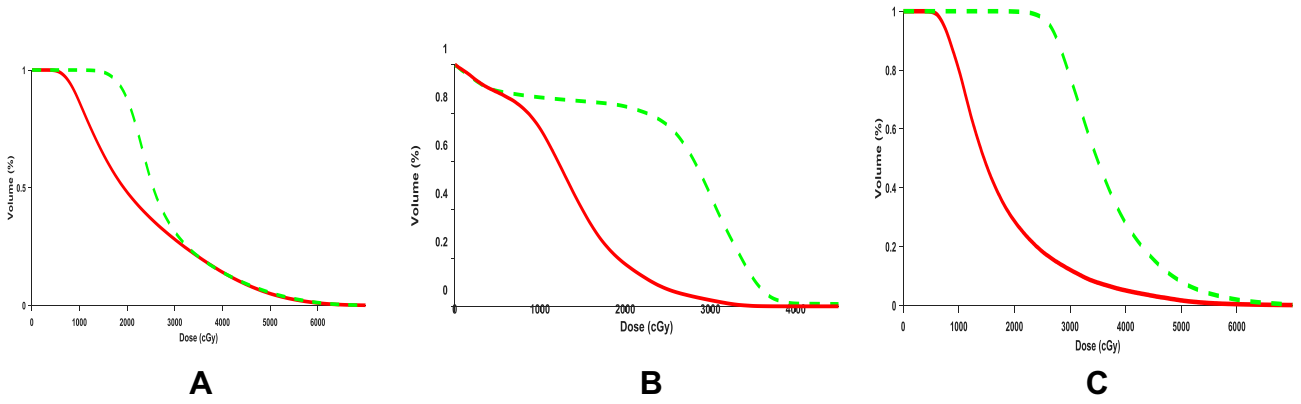

Figure 1 (**A**) Comparison of parotid gland DVH showing that the parotid gland received a higher dose in MA plans. (**B**) Comparison of spinal cord DVH showing that spinal cord received a higher dose in MA plans. (**C**) Comparison of mandible joint DVH showing that mandible joint received a higher dose in MA plans. The red line represents the AU plan and the green line represents the MA plan.

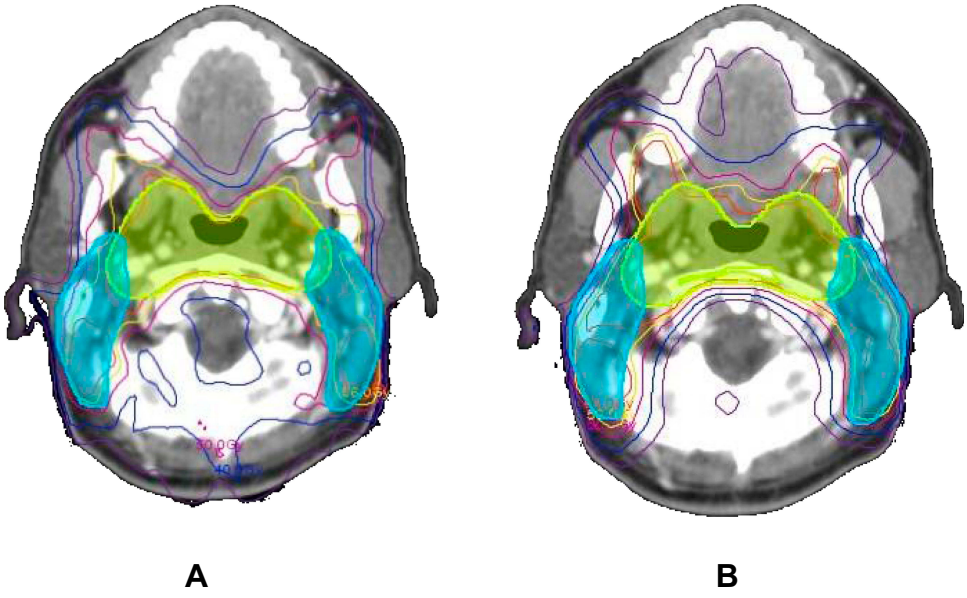

Figure 2 (**A**) Dose distribution of MA plans (**B**) Dose distribution of AU plans PCTV1, PCTV2.

a high-quality treatment plan that meets clinical needs without any human intervention and can also be used as a starting point for further manual adjustment.[19] In addition, Zhu Jian et al[22] studied the ART plan dose evaluation method based on the script function in the Pinnacle planning system, and concluded that the ART plan evaluation method is accurate, simple, and convenient, and improves the flexibility and accuracy of evaluating the dose of adaptive radiotherapy; it can also provide the technical support for clinical and scientific research work.

Manual adjustment of nasopharyngeal carcinoma requires the high-level experience of physicists. As shown in Figure 1, the parotid received a lower dose in a low-dose area, which shows that for low-dose areas, there is still some room to improve after manual optimization. The spinal cord received a lower mean dose because the physicist focused on the maximum dose in the spinal cord when manually optimizing. When beginning optimization, physicists need to ensure the target coverage; however, due to limited time the organ limit is relatively loose, and physicists cannot guarantee that the low-dose limit is maintained in every organ. This may result in some low tolerance dose OARs (like mandible joint) receiving higher doses. However, all of the 105 manual plans have met the clinical requirements, but still can be improved. A study on IMRT breast cancer[21] showed that an automatic planning system provided great help to less experienced

Table 7 CI and HI for MA Plans in Eclipse and Pinnacle TPS

HI	Eclipse	Pinnacle	*P*
PGTV	0.0777±0.006	0.0858±0.006	*P*=0.24
PCTV1	0.0704±0.005	0.0644±0.003	*P*=0.13
PCTV2	0.1548±0.023	0.1651±0.047	*P*=0.62
PCTVn	0.2361±0.030	0.2672±0.032	*P*=0.15
CI			
PGTV	1.36±0.11	1.37±0.21	*P*=0.46
PCTVn	1.54±0.23	1.52±0.25	*P*=0.21

Table 8 Max Dose of Serial Organs for MA Plans in Eclipse and Pinnacle TPS cGy, (X± χ)

OARs	Eclipse	Pinnacle	*P*
Brain stem	4933.3±452.7	5056.9±239.8	*P*=0.5
Spinal cord	3854.1±297.3	3875.5±537.3	*P*=0.5
Left lens	471.3±159.0	456.7±35.5	*P*=0.3
Right lens	455.5±164.1	427.3±64.4	*P*=0.5
Left temporal lobe	2428.3±1661.7	2338.8±1285	*P*=0.3
Right temporal lobe	2564.6±1865.4	2512.8±1454.5	*P*=0.2
Left optic nerve	2368.3±1692.2	2318.1±1140.3	*P*=0.2

Table 9 Mean Dose of Parallel Organs Ofor MA Plans in Eclipse and Pinnacle TPS (cGy, X± χ)

OARs	Eclipse	Pinnacle	*P*
Oropharynx	3348.9±313.4	3326.7±272.4	*P*=0.8
Left parotid gland	2847.12±313.2	2913.8±467.3	*P*=0.6
Right parotid gland	2872.68±334.6	2856.4±475.7	*P*=0.3
Left mandible	3926.43±432.2	3826.8±922.2	*P*=0.07
Right mandible	3856.05±401.9	3776.8±819.9	*P*=0.08
Left mandible joint	3637.1±631.4	3724.6±854.4	*P*=0.2
Right mandible joint	3644.5±709.2	3705.3±792.3	*P*=0.1
Normal tissue (NT)	946.1±110.2	982.4±118.8	*P*=0.6

physicists, but for physicists with rich experience, the results showed small differences between AU and MA plans. If there are enough time and experience for physicists to adjust treatment planning, physicists can generate treatment plans with the same high quality as automatic systems.

An AU plan can guarantee the premise of the target coverage as long as tightening all OARs' dose limit, it can also reduce the various dose distributions between the treatment plans in quality assurance during limited time, and this is the biggest advantage of AU planning. On the other hand, the survival period of head and neck cancer patients is relatively long; clinically, doctors have paid more attention to improving the quality of patients' life, and the results of this study can provide a quantitative reference to the clinical evaluation.

Bo Penggang[23] and He Genbo[20] also studied automatic IMRT planning for nasopharyngeal carcinoma and got good results, the former is a combination of the C++ language and the Pinnacle[3] treatment plan system script, and the latter is programmed to run automatically. This study uses an automatic program system mdaccAutoPlan, without programming with a large number of patients treated plan collection to be the database, Bo Penggang et al[23] and He et al[20] has the collection of 10 cases, this study collected 105 cases of patients, which can reduce the random error of data.

In the choice of the automatic IMRT plan angle, unlike Zhang et al,[24] in order to reduce the effect of AU planning and MA planning results due to the different field angle, this study did not use the angular optimization function in the mdaccAutoPlan automatic planning system, the NPC target distribution of AU plan and MA plan in this study were unified by 7 equipartition field, whether the optimization results with different beam number and angle will be better? This is our next step to continue the study.

Deficiency, the AU plan and the MA plan were calculated using two planning systems (Pinnacle and Eclipse, respectively), we have compared the dose of MA plans between Pinnacle and Eclipse TPS, as shown in Tables 7–9, there is no significant differences between these two systems, and research of Lopez et al[25] also have shown that the difference in dose calculation between the two planning systems of Pinnacle and Eclipse is less than 3%, the AU and MA plans are comparable. However, this study only compared the optimization results of the two systems, but not for the research on the algorithms and clinical use, which will be the direction of our further research. We have not yet performed a quality assurance of AU plans yet; we will also do further research to see if it can be used in clinical applications.

Conclusion

Comparison of AU and MA plan for nasopharyngeal cancer shows a very small dosimetric difference in target coverage, but the AU plan has clear advantages in protecting OARs as well as saving labor time. It may be another option for the clinical implementation of nasopharyngeal carcinoma IMRT treatment planning.

Disclosure

The abstract has been presented previously as an e-poster in ESTRO 2017. The authors report no conflicts of interest in the work.

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