

Comparison of Second Cancer Risk in Patients with Liver Cancer Treated By Stereotactic Body Radiotherapy and Three-Dimensional Conformal Radiotherapy

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Abstract

Background: Stereotactic body radiotherapy (SBRT) is suggested to pose higher second cancer risk than conventional three-dimensional conformal radiotherapy (3D-CRT) for generating greater scatter/leakage dose to distant organs. Epidemiological reports indicate the need to include primary beam effect in risk assessment because of its great contribution to total cancer risk.

Objectives: To determine the second cancer dosimetric index, organ equivalent dose (OED), for organ in treatment field (planning target volume, PTV), beam border (uninvolved liver), and distant area (stomach and pancreas) in patients with liver cancer treated either by Cyberknife SBRT (Cyber-SBRT) or 3D-CRT.

Methods: Treatment plans for seven patients were optimized and a prescription dose of 45 Gy were delivered in 15 Gy x3 fractions for Cyber-SBRT and 1.8 Gy x25 fractions for 3D-CRT. OED for primary beam was calculated from differential dose volume histogram. Image-guided dose and scatter/leakage dose from each treatment were measured in Rando phantom using thermoluminescence dosimeters.

Results: For primary beam component, OEDs of PTV were comparable for both treatments ($p=0.00003$). In organs outside the treatment field, Cyber-SBRT generated much lower OEDs than 3D-CRT ($p \leq 0.059$). OEDs for scatter/leakage component were smaller for 3D-CRT but their contributions to total OEDs were $<1\%$. OED from image-guided procedure in Cyber-SBRT was relatively small. In Overall, total OEDs were comparable between Cyber-SBRT and 3D-CRT.

Conclusion: Total OEDs of normal tissues from both treatments were comparable or apparently lower for SBRT than 3D-CRT ($p \geq 0.20$) while total OED of PTV from Cyber-SBRT is slightly higher than that of 3D-CRT ($p<0.05$).

Keywords: SBRT, 3D-CRT, second cancers, organ equivalent dose

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Background

In the past, radiotherapy of liver cancer played only a palliative role because of normal liver toxicity prohibiting the prescription of curative dose to the tumor. This is mainly due to the organ motion with respiration and the poor dose targeting by the old radiotherapeutic unit. As a consequence, large volume of liver is included in the treatment portal⁽¹⁾. With the development of three-dimensional conformal radiotherapy (3D-CRT), better dose targeting allows higher tumor dose and spares larger liver volume, to reduce radiation-induced liver toxicity⁽²⁾. However, organ motion is still a problem needed to be corrected. Recently, the Cyberknife Radiosurgery System in conjunction with the Synchrony[®] Respiratory Tracking System receives great interest in treating the primary liver cancer and liver metastases. The system can deliver very high dose to tumor target with extreme accuracy using a very accurate image to image correlation algorithm. Motion management is conducted by the Synchrony[®] Respiratory Tracking System which enables the radiation beam to track tumor movement in real time. This technique of treatment is called stereotactic body radiotherapy (SBRT). The efficacy of advanced radiotherapy technique has led to a higher cure rate for cancer and a longer patient survival time. Outcomes of SBRT in treating 62 patients with 106 liver lesions during 2006-2010 were reported by Stenmark et al⁽³⁾. Two-year overall survival rates for primary and metastatic tumor were 29% and 63% respectively. Treatment-induced secondary cancer has become a point of concern. Long-term survival from SBRT was also reported by Guvén et al⁽⁴⁾. Nine patients who were cured by SBRT were reported to survive 5-14 years without recurrences. However, two verified and one suspected secondary cancers occurred in organs close to the irradiated target at 2 and 8 years after the treatment.

In achieving a good target dose conformity, the modern radiotherapeutic systems utilize more small

beams/fields in a great number of direction to deliver the prescribed target dose in many more monitor units (MUs) comparing to the conventional 3D-CRT. By this technique of treatment delivery, higher peripheral doses to nearby and distant organs can be expected due to higher scatter/leakage radiations as a consequence of increase treatment MU or longer beam on time. The concept of peripheral dose for second cancer risk assessment after radiotherapy has been challenged by several epidemiological reports to address a significant frequency of radiation-induced in-field sarcoma in addition to carcinoma at the beam border⁽⁵⁾. This indicates the need to include the primary beam component in addition to leakage/scatter component in second cancer risk assessment.

Schneider et al⁽⁶⁾ proposed an organ equivalent dose (OED) concept describing the second cancer risk as a non-linear function of radiation dose. This allows the assessment of second cancer risks from primary as well as scatter/leakage components. The OED defined plateau model as proposed by Schneider et al was adopted for this study because a plateau dose response relationship was reported for second cancer developed after radiotherapy and also for radiation-induced cancer in atomic bomb survivors⁽⁷⁾. The OED was determined as follow.

$$OED = \frac{1}{V_T} \sum_i DVH(D_i) \frac{(1-e^{-\delta D_i})}{\delta} \quad \text{Equation 1}$$

Where DVH(D_i) is the volume of tissue corresponding to dose D_i , V_T is total volume of organ and δ is plateau model parameter describing cell killing and cell repopulation (0.139 Gy^{-1})⁽⁸⁾.

The aim of this study is to compare the second cancer risks in planning target volume (PTV), organ at beam border i.e. uninvolved liver, and distant organs such as stomach and pancreas in patients with primary liver cancer and liver metastases treated either by Cyberknife stereotactic body radiotherapy (Cyber-SBRT) or 3D-CRT.

Materials and methods

Two treatment plans for Cyber-SBRT and 3D-CRT for each of the seven patients with primary liver cancer or liver metastases were designed based on dose constraints to critical organ including esophagus, heart, spinal cord liver and kidney suggested by Emami et al⁽⁹⁾ for 3D-CRT and by Timmerman⁽¹⁰⁾ for Cyber-SBRT. The gross tumor volume (GTV) varied from 1.58 to 169.0 cm³ with a median of 19.13 cm³. The PTVs for Cyber-SBRT were defined as the GTV plus 1 mm. For 3D-CRT all PTVs were defined as GTV plus 3 mm in dorsoventral and left-right axis and 7 mm in cranial-caudal axis. On average, a dose of 43.46 Gy (ranges 36-50.4 Gy) was prescribed to treat the tumor in 12-15 Gy/fraction for Cyber-SBRT and 1.8 Gy/fraction for 3D-CRT. In this study the treatment plans of Cyber-SBRT were delivered by Cyberknife G4 system with 6 MV photons, the collimator size varied from 1 cm to 4 cm, number of beam orientations were 190-335 and number of image-guided beam were 456-816. 3D-CRT were delivered by Variant Clinac 2100c with 6, 10 MV photons where appropriated, the collimator size varied from 3.6x3.6 cm² to 11x9 cm² and number of beam orientations are 3-6.

The total organ-equivalent dose (OED_T) for Cyber-SBRT and 3D-CRT were determined according to the equation below.

OED_T for Cyber-SBRT

$$OED_T = OED_{\text{prim}} + OED_{\text{imaging}} + OED_{\text{scatter/leakage}} \quad \text{Equation 2}$$

OED_T for 3D-CRT

$$OED_T = OED_{\text{prim}} + OED_{\text{scatter/leakage}} \quad \text{Equation 3}$$

Where OED_{prim} is the OED for the primary beam component, OED_{image} is the OED due to image-guided dose in Cyber-SBRT treatment and OED_{scatter/leakage} is the OED generated by scatter radiation and collimator leakage.

OED_{prim} was calculated as following equation

$$OED_{\text{prim}} = \frac{1}{V_T} \sum_i dDVH(D_i) \frac{(1-e^{-\delta D_i})}{\delta} \quad \text{Equation 4}$$

Where dDVH(D_i) is differential dose volume histogram in corresponding to dose D_i. To determine OED_{prim}, V_T, dDVH(D_i) and D_i for each interested organ were obtained from treatment planning system (TPS). The volume dose pair [dDVH_i, D_i] yielded an OED due to the physical dose component. To account for the biological difference in different dose fractions used for Cyber-SBRT and 3D-CRT, All D_i's from DVH data were normalized to an equivalent dose in 1.8 Gy/fraction (EQD_{1.8}).

$$EQD_{1.8} = D_i \left[\frac{d_i + \alpha/\beta}{1.8 + \alpha/\beta} \right] \quad \text{Equation 5}$$

Where D_i was the dose associated with the dDVH_i and d_i = D_i/fraction number. α/β were 15 Gy for PTV⁽¹¹⁾, 1 Gy for uninvolved liver⁽¹²⁾, 3 Gy for pancreas⁽¹³⁾ and 4 Gy for stomach⁽¹³⁾.

For OED_{image}, radiation dose from image-guided (D_i) were measured by TLD-100H chips in the Rando phantom. The exposure technique was set at 125 kV 30 mAs⁽¹⁴⁾. Two TLD chips were placed at each point of measurement to obtain the imaging dose/exposure (Figure 1). The organs of interest were located in Rando phantom according to the guide line suggested by Scalzetti et al⁽¹⁵⁾. Imaging dose for each patient was calculated based on the actual number of exposure received. The measurement dose were normalized to an equivalent dose in 1.8 Gy/fraction (EQD_{1.8}) and used for OED calculation (Equation 6).

$$OED_{\text{image}} = \frac{(1-e^{-\delta D_i})}{\delta} \quad \text{Equation 6}$$

For OED_{scatter/leakage}, radiation dose from scatter/leakage for each treatment plan was measured in Rando phantom using TLD-700 rods. To measure the scatter/leakage dose, the phantom was set at the



same position as the patient was treated. Irradiation was delivered according to the patient treatment plan. The scatter/leakage dose was measured at 8 points outside treatment volume (Figure 1). The average of all the measured points in the Rando phantom was regarded as an estimate of scatter/leakage dose to the whole body⁽¹⁶⁾. Multiplication of the whole body dose in Gy/MU with the total treatment MU yielded the scatter/leakage dose to total body of individual patient. The $OED_{\text{scatter/leakage}}$ for organ of interest was calculated using the equation 7.

$$OED_{\text{scatter/leakage}} = \frac{V_T}{V_{WB}} \frac{(1 - e^{-\delta D_i})}{\delta} \quad \text{Equation 7}$$

$$V_{WB} = \frac{WB}{G} \text{ (cm}^3\text{)} \quad \text{Equation 8}$$

Where, V_{WB} was the volume of whole body receiving scatter or leakage of D Gy. V_{WB} was calculated from the patient whole body weight (WB) in g with a body density (G) of 1.07 g/cm³ for male and

1.04 g/cm³ for female⁽¹⁷⁾. V_T was the volume for organ of interest.

This study used a paired Student t-test to analyze the difference in OEDs from Cyber-SBRT and 3D-CRT. All the statistical tests were 2-tailed with $p \leq 0.05$ was considered statistically significant.

Results

OEDs in organ/region of interest from Cyber-SBRT and 3D-CRT are presented in Tables 1 and 2. For primary beam component, OED_{prim} of PTV from the Cyber-SBRT plan was 0.16% greater than that of the 3D-CRT plan ($p=0.00003$). While other organs including liver, pancreas and stomach, Cyber-SBRT plan generated less OED_{prim} s than 3D-CRT ($p = 0.059, 0.01$ and 0.04 , respectively). Image-guided dose from Cyber-SBRT distributed uniformly over the entire imaging frame covering all regions/organs in this study, i.e. within $\pm 0.813\%$. OED_{image} were made different by / values of different organs. For PTV and liver, OED_{image} from image-guided doses contributed in between

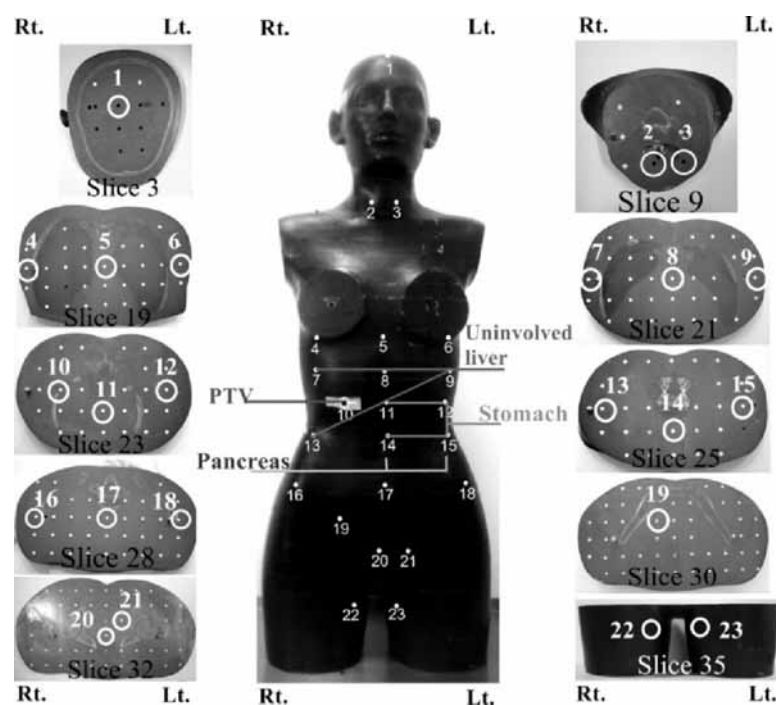


Figure 1 Image-guided measurement points are number 7-15. Scatter/leakage dose measurement points are number 1-3 and 19-23.

5%-8% of the OED_T . For distant organs such as pancreas and stomach, $OED_{image's}$ of image-guided doses were major components accounted for 69%-84% of OED_T .

Cyber-SBRT produced whole body scatter/leakage dose 2.41 times greater than that by 3D-CRT ($p=0.003$). Comparison of $OED_{scatter/leakage}$ data between 3D-CRT and Cyber-SBRT, we observed that Cyber-SBRT generated comparable $OED_{scatter/leakage}$ to PTV but greater $OED_{scatter/leakage}$'s to uninvolved liver ($p=0.002$) pancreas ($p=0.001$) and stomach ($p=0.001$). Despite this difference, $OED_{scatter/leakage}$'s for scatter/leakage component from 3D-CRT and Cyber-SBRT had the smallest contribution to the total OED.

The average of total OEDs for 3D-CRT, OED_{prim} contributed to almost all of the OED_T , i.e. > 99%. The $OED_{scatter/leakage}$ was negligible small. This was in contrast to the Cyber-SBRT technique, OED_{prim} played a significant part in PTV (94.96%), and uninvolved liver (91.60%) followed by $OED_{image's}$, 5.04% and 8.30% for PTV and uninvolved liver, respectively. The scatter/leakage contribution was minimal for these regions. In stomach and pancreas, OED from image-guided dose were the major components of the OED_T , 83.35% contribution for pancreas and 69.25% for stomach. Again, scatter/leakage radiation played a minor part (Table 1-2).

Table 1 Total OEDs for organ/region of interest from Cyber-SBRT.

Organ/region	Total OED, Gy	Primary beam		Scatter/leakage		Image-guided	
		OED, Gy	% of total	OED, Gy	% of total	OED, Gy	% of total
PTV	7.576 (0.0791)	7.194 (0.001)	94.958 (0.99)	1.21×10^{-4} (1.53×10^{-4})	0.002 (0.002)	0.383 (0.080)	5.041 (1.001)
Uninvolved liver	2.760 (1.211)	2.567 (1.213)	91.600 (3.997)	2.27×10^{-3} (6.97×10^{-4})	0.098 (0.062)	0.190 (0.045)	8.303 (3.967)
Pancreas	0.461 (0.294)	0.142 (0.301)	16.630 (27.764)	8.76×10^{-5} (2.46×10^{-5})	0.024 (0.013)	0.319 (0.070)	83.347 (27.755)
Stomach	0.737 (0.762)	0.403 (0.780)	30.626 (31.724)	6.23×10^{-4} (2.87×10^{-4})	0.127 (0.075)	0.334 (0.072)	69.247 (31.666)

Table 2 Total OEDs for organ/region of interest from 3D-CRT.

Organ/region	Total OED, Gy	Primary beam		Scatter/leakage	
		OED, Gy	% of total	OED, Gy	% of total
PTV	7.182 (0.003)	7.182 (0.003)	99.999 (0.001)	7.93×10^{-5} (7.74×10^{-5})	0.001 (0.001)
Uninvolved liver	3.023 (1.109)	3.022 (1.108)	99.968 (0.013)	9.08×10^{-4} (2.67×10^{-4})	0.032 (0.013)
Pancreas	0.571 (0.546)	0.571 (0.546)	99.986 (0.012)	3.66×10^{-5} (1.38×10^{-5})	0.014 (0.012)
Stomach	0.981 (0.732)	0.981 (0.732)	99.947 (0.052)	2.78×10^{-4} (1.78×10^{-4})	0.053 (0.052)



In comparison between treatments, total OED for PTV generated by Cyber-SBRT was 5.2% larger than that by 3D-CRT ($p=0.00001$). On the contrary, total OEDs for liver, pancreas, stomach tended to be lower than those generated by 3D-CRT, i.e. 9.54%, 23.90%, 33.06%, respectively (Table 3). In these organs, extra image-guided dose and greater scatter/leakage radiation from Cyber-SBRT were compensated by lower OED_{prim} from the primary beam component to render the total OEDs comparable or apparently lower than those from 3D-CRT ($p \geq 0.29$).

Discussion

Total OEDs of normal tissues from both treatments were comparable or apparently lower for Cyber-SBRT than 3D-CRT. The observation could be explained on the basis of superior dose-targeting and rapid dose fall off characteristics of Cyber-SBRT in reducing the primary beam OED. This helps compensating for OED due to image-guided dose and OED from scatter/leakage component to make the total OED not much different or apparently less than that of 3D-CRT. However, OED_T in PTV for Cyber-SBRT plan was 5.2% greater than that of the 3D-CRT plan ($p=0.00001$).

Finding from this study suggest that doses from image-guided system of Cyber-SBRT make the major component of the total OED. The observation of large contribution of doses from image-guided system of Cyber-SBRT to total OEDs of organs such as stomach and pancreas which received lower doses than liver i.e. 83.35% for pancreas and 69.25% for stomach suggests a need to optimize the exposure technique or to minimize the number of exposures in order to lower the imaging doses thereby reducing the OED_{image} .

On the other hand, OED_{prim} for PTV of the Cyber-SBRT larger than the OED_{prim} for 3D-CRT raises a question concerning the validity of the plateau model in predicting second cancer risks for PTV. Since the $EQD_{1.8}$ for Cyber-SBRT was 1.71 times greater than that by 3D-CRT, i.e. 79.06 Gy for Cyber-SBRT and 46.22 Gy for 3D-CRT. In principle, much less mutant cells from Cyber-SBRT comparing to 3D-CRT will survive to induced second cancer years later. On this basis, a log-exponential model describing cell killing at high dose⁽¹⁸⁾ should be more appropriate for calculation of OED_{prim} for PTV.

Table 3 Comparison between total OEDs from Cyber-SBRT and 3D-CRT.

Organ/region	Cyber-SBRT \bar{X} (SD), Gy	3D-CRT \bar{X} (SD), Gy	$\frac{OED_{SBRT}}{OED_{3DCRT}}$	[95% C.I.]	P-Value
PTV OED	7.576	7.182 (0.079)	1.055 (0.003)	[1.0341.075]	0.00001
Uninvolved liver OED	2.760 (1.211)	3.023 (1.109)	0.913	[-0.2082.034]	0.203
Pancreas OED	0.461 (0.294)	0.571 (0.546)	0.807	[-1.4443.058]	0.338
Stomach OED	0.737 (0.762)	0.981 (0.732)	0.752	[-1.7483.251]	0.285

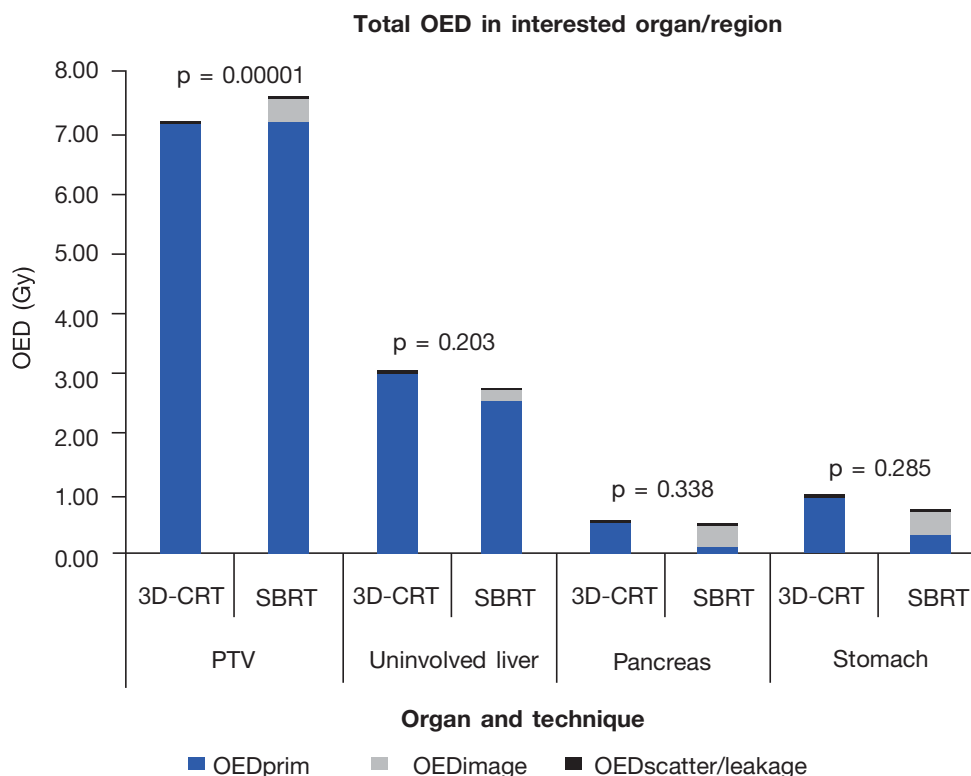


Figure 2 Total OED from Cyber-SBRT and 3D-CRT in organ/ region of interest.

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การเปรียบเทียบความเสียหายต่อมะเร็งทุดีใน ผู้ป่วยมะเร็งตับจากการบำบัดโดยรังสีรักษาแบบ แบบทั่วร่างกายและรังสีรักษาสามมิติ

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บทคัดย่อ

บทนำ: รังสีรักษาร่วมพิภพแบบทั่วร่างกาย (SBRT) อาจจะทำให้เกิดมะเร็งทุดีมากกว่ารังสีรักษาสามมิติ (3D-CRT) เนื่องจากมีปริมาณรังสีกระจายและรังสีรั่วไหลมากกว่า แต่ผลการวิจัยทางระบาดวิทยาบ่งชี้ว่าการประเมินความเสี่ยงต่อมะเร็งทุดีควรพิจารณาถึงผลของรังสีปริมาณรวมด้วยเพราะเป็นปัจจัยหลักในการก่อให้เกิดมะเร็งทุดี

วัตถุประสงค์: เพื่อเปรียบเทียบดัชนีชี้ความเสี่ยงของมะเร็งทุดี (OED) ในปริมาณของรังสีบำบัด (PTV), อวัยวะที่ติดกับขอบลำรังสี (เนื้อตับปกติ) และ อวัยวะที่อยู่ห่างจากลำรังสี (ตับอ่อน และกระเพาะอาหาร) ในผู้ป่วยมะเร็งตับจากการบำบัดด้วยรังสีรักษาร่วมพิภพแบบทั่วร่างกายด้วยเครื่อง Cyberknife (Cyber-SBRT) หรือ 3D-CRT

วิธีการศึกษาวิจัย: คำนวณแผนการรักษาที่เหมาะสมสำหรับผู้ป่วยจำนวน 7 รายด้วยวิธี Cyber-SBRT และวิธี 3D-CRT โดยฉายรังสีปริมาณ 45 Gy แบบ 15 Gy x 3 ครั้ง สำหรับวิธี Cyber-SBRT และ 1.8 Gy x 3 ครั้ง สำหรับวิธี 3D-CRT คำนวณ OED ของรังสีปริมาณรวมจาก differential dose volume histograms และวัดปริมาณรังสีจากระบบภาพนำวิถีของ Cyber-SBRT, รังสีกระจายและรังสีรั่วไหล จากแต่ละแผนการรักษาด้วย thermoluminescence dosimeter ใน Rando phantom

ผลการศึกษา: OEDจากรังสีปริมาณรวมของทั้งสองเทคนิคการรักษาใน PTV มีค่าใกล้เคียงกัน ($p=0.00003$) แต่ในอวัยวะอื่นๆ ค่า OED ของ Cyber-SBRT มีค่าต่ำกว่า 3D-CRT ($p \leq 0.059$) ส่วน OED จากรังสีกระจายและรังสีรั่วไหลของ 3D-CRT มีค่าต่ำกว่า Cyber-SBRT แต่ OED จากรังสีกระจายและรังสีรั่วไหลมีค่า $<1\%$ ของ OED รวม และ OED จากระบบภาพนำวิถีของ Cyber-SBRT มีค่าน้อย เมื่อคิดรวมทั้งสามส่วนเป็น OED รวม พบว่า OED รวมมีค่าใกล้เคียงกันทั้งสองเทคนิคการรักษา

สรุป: OED ในเนื้อเยื่อปกติโดยรอบ PTV จากการบำบัดทั้งสองวิธีมีค่าใกล้เคียงกัน Cyber-SBRT มีค่าต่ำกว่า 3D-CRT เล็กน้อยแต่ไม่ต่างกันทางสถิติ ($p > 0.2$) แต่ OED ของ PTV จากการบำบัดด้วยวิธี Cyber-SBRT มีค่าสูงกว่า 3D-CRT เล็กน้อย ($p < 0.05$)

คำสำคัญ: SBRT, 3D-CRT, มะเร็งทุดี, organ equivalent dose

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