

1 **Is stereotactic CyberKnife radiotherapy or multicatheter HDR brachytherapy the**  
2 **better option for accelerated partial breast irradiation?**

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14 **Dosimetric comparison of CyberKnife and HDR BT in APBI**

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## Abstract

21 **Objective:** To compare dosimetrically the stereotactic CyberKnife (CK) therapy and  
22 multicatheter high-dose-rate (HDR) brachytherapy (BT) for accelerated partial breast  
23 irradiation (APBI).

24 **Methods:** Treatment plans of twenty-five patients treated with CK were selected and additional  
25 plans using multicatheter HDR BT were created on the same CT images. The prescribed dose  
26 was 6.25/25 Gy in both plans to the target volume (PTV). The dose-volume parameters were  
27 calculated for both techniques and compared.

28 **Results:** The D90 total dose of the PTV was significantly lower with CK than with HDR BT,  
29 D90 was 25.7 Gy and 27.0 Gy ( $p < 0.001$ ). However, CK plans were more conformal than BT,  
30 COIN was 0.87 and 0.81 ( $p = 0.0030$ ). The V50 of the non-target breast was higher with CK  
31 than with BT: 10.5% and 3.3% ( $p = 0.0010$ ), while there was no difference in the dose of the  
32 contralateral breast and contralateral lung. Dose to skin, ipsilateral lung and ribs were higher  
33 with CK than with BT: D<sub>1</sub> was 20.6 Gy vs. 11.5 Gy ( $p = 0.0018$ ) to skin, 11.4 Gy vs. 9.6 Gy  
34 ( $p = 0.0272$ ) to ipsilateral lung and 18.5 Gy vs. 12.3 Gy ( $p = 0.0013$ ) to ribs, while D<sub>0.1</sub> to heart  
35 was lower, 3.0 Gy vs. 3.2 Gy ( $p = 0.0476$ ), respectively.

36 **Conclusions:** Multicatheter HDR BT yields more advantageous plans than stereotactic  
37 CyberKnife treatment in accelerated partial breast irradiation, except in terms of dose  
38 conformality and the dose to the heart. There was no difference in the dose of the contralateral  
39 breast and -lung.

40 **Keywords:** breast cancer; CyberKnife therapy; multicatheter high-dose-rate brachytherapy;  
41 accelerated partial breast irradiation

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## 44 **Introduction**

45 Over the last decades, breast-conserving surgery followed by postoperative radiotherapy  
46 became the standard of care for the treatment of early-stage breast carcinoma [1-2]. Nowadays,  
47 accelerated partial breast irradiation (APBI) is an attractive alternative to conventional whole  
48 breast radiotherapy for selected group of patients [3]. Moreover, it has been demonstrated that  
49 higher doses to the tumour bed significantly reduce the local recurrence rate [4-7]. The number  
50 of techniques and devices used to deliver APBI has increased dramatically in recent decades in  
51 an attempt to create more conformal, homogenous, and reproducible dose distributions as well  
52 as to provide shorter, more convenient treatment schedules. Such as EBRT using 3D conformal  
53 (3D-CRT), intensity-modulated (IMRT) technique or arc-therapy (IMAT) [8], helical  
54 tomotherapy (HT) [9], stereotactic radiotherapy with CyberKnife (CK) [10-14], protontherapy  
55 (PT) [15], as well as high-dose-rate (HDR) or pulsed-dose-rate (PDR) balloon [16] or  
56 multicatheter BT [17] or using Strut Adjusted Volume Implant (SAVI) [18]. All of these  
57 techniques offer equal convenience but differ substantially in dose distribution and treatment  
58 delivery [19].

59 While the dosimetric parameters which affect toxicity have been thoroughly  
60 investigated for BT techniques [20-21], and the use of interstitial BT is supported by over ten  
61 years of follow-up data demonstrating excellent local control and minimal long-term toxicity  
62 when established dosimetric guidelines are used for planning [22-26], EBRT is associated with  
63 less available follow-up data, and currently no standardized, evidence-based treatment planning  
64 guidelines exist for this technique. Therefore, a detailed dosimetric analysis comparing the  
65 rapidly developing EBRT techniques to the pivotal BT modality is essential.

66 In our previous study we compared the dose distributions of 3D-CRT and three different  
67 intensity-modulated APBI technique: step and shoot and sliding window IMRT and IMAT in  
68 40 patients [8]. Goggin et al. [27] compared 3D-CRT and CK with circular (Iris) and multi-leaf  
69 collimators in case of 9 patients. Xu et al. [28] and Rault et al. [29] compared the dosimetry of  
70 CK, 3D-CRT and IMRT plans, while Bonfantini et al. [30] made a dosimetric comparison of  
71 CK, 3D-CRT and IMAT plans.

72 Khan et al. [31] investigated the dosimetric differences among MammoSite balloon BT,  
73 3D-CRT and IMRT for 15 cases. Previously, we examined the dosimetry of organs at risks  
74 (OARs) in multicatheter HDR BT against IMRT for 34 cases [32]. Hoekstra et al. studied the  
75 long-term risk of secondary cancer calculating Lifetime Attributable Risks using a Rando breast

76 phantom in multicatheter HDR BT, 3D-CRT, CK, IMAT and whole breast irradiation (WBI)  
77 [33].

78 Recently, stereotactic CyberKnife therapy and interstitial multicatheter high-dose-rate  
79 brachytherapy are considered as the most advantageous APBI techniques in early-stage breast  
80 cancer, at the same time their dosimetric comparison is not available in the literature. At our  
81 institute, both state-of-the art techniques are available. To take the advantage of this situation,  
82 the aim of the present study is a detailed dosimetric comparison of CK treatment and HDR  
83 multicatheter BT for APBI.

## 84 **Materials and methods**

### 85 *Stereotactic CyberKnife radiotherapy*

86 Twenty-five CK plans of patients with early-stage breast cancer treated at our institute were  
87 included in this study. Selection criteria for treatment were the following: unifocal tumour;  
88 primary tumour size by final pathology <30 mm (pT1); microscopically negative surgical  
89 margins (>2 mm); histologic grade 1–2; pN0 axillary status, age over 50 years, without  
90 extensive intraductalis component or lymph vessel invasion [34].

91 CK treatments were performed with non-coplanar fields using CyberKnife M6 linear  
92 accelerator (Accuray, Sunnyvale, CA, USA). Titanium surgical clips were implanted into the  
93 tumour bed during the surgery to help contouring the lumpectomy cavity and defining the  
94 clinical target volume (CTV), and additional 4 fiducial gold markers were placed around the  
95 cavity with US guidance for tracking purpose. The CTV was extended by an isotropic 2 mm  
96 margin to create the planning target volume (PTV), and the fractional prescribed dose was 6.25  
97 Gy. A total of 4 fractions (total dose 25 Gy) were given every consecutive day. For treatment  
98 planning Accuray Precision 1.1 treatment planning system (TPS) (Accuray, Sunnyvale, CA,  
99 USA) was used. The dose was prescribed to the 80–85% isodoses (*Fig 1.a*). The relative volume  
100 of the PTV receiving at least the prescribed dose (V100) had to be at least 95%. The detailed  
101 description of our treatment method can be found in our previous publication [14].

### 102 *Multicatheter brachytherapy*

103 On the CT series made for CK treatment planning, additional plans using virtual interstitial  
104 catheters were created using the same contour set. The CTV was identical to the PTV, and the  
105 prescribed dose was also the same as in CK, 25 Gy in 4 treatment fractions giving 6.25 Gy two  
106 times a day using an HDR Ir-192 radioactive source. HIPO (Hybrid Inverse Planning

107 Optimization) optimisation method was used to achieve the optimal dose distribution, where  
108 the target volume coverage by the reference dose is at least 90%, while keeping the dose non-  
109 uniformity ratio (DNR) less than 0.35 (*Fig 1.b*). For planning the Oncentra Prostate v3.1 TPS  
110 (Elekta Brachytherapy, Veendendaal, The Netherlands) was used. The detailed description of  
111 our treatment method can be found in our previous publications [17,22-25].

## 112 *Dosimetric comparison*

113 The absolute and the relative ( ) total dose were calculated for both techniques. The  
114 following dose-volume parameters were used for quantitative evaluation of plans:

115 **D90:** the minimum dose delivered to 90% of the PTV;

116 **COIN:** conformal index [35];

117 **V50(non-target breast):** the relative volume in percentage of non-target breast  
118 receiving at least the 50% of the prescribed dose;

119 **D<sub>1</sub>(x), D<sub>0.1</sub>(x):** the minimal dose of the most exposed 1 and 0.1 cm<sup>3</sup> of *the critical organ*

120 *x*,

121 where *x*: *contralateral breast (contralat breast), skin, ipsilateral lung (ipsilat lung),*  
122 *contralateral lung (contralat lung), heart and ribs.*

123 Wilcoxon Matched Pairs Test was used (Statistica 12.5, StatSoft, Tulsa, OK, USA) to  
124 compare dose-volume parameters of CK and HDR BT techniques.

## 125 **Results**

126 The mean volume of the CTV and PTV was 51.1 cm<sup>3</sup> (27.0-81.5 cm<sup>3</sup>) and 71.6 cm<sup>3</sup>  
127 (41.1-105.6 cm<sup>3</sup>). The ratio of the CTV to the whole breast volume was 0.09 (0.05-0.19). Eleven  
128 patients had tumour in her left breast and fourteen in the right one.

129 We found that D90 total dose of the PTV was significantly lower with CK than with  
130 HDR BT, it was 25.7 Gy and 27.0 Gy (p<0.001). However, CK plans were more conformal  
131 than BT, the COIN was 0.87 and 0.81 (p=0.0030), respectively.

132 In our comparison, the V50 of the non-target breast was higher with CK than with BT:  
133 10.5% and 3.3% (p=0.0010), while there was no statistical difference in the doses of the  
134 contralateral breast (D<sub>1</sub>: 0.5 vs. 0.4 Gy, P=0.3112) and contralateral lung, (D<sub>1</sub>: 0.7 vs. 0.7 Gy,  
135 p=0.5345).

136 In terms of the other OARs, dose to skin, ipsilateral lung and ribs were higher with CK  
137 than with BT: D<sub>1</sub> was 20.6 Gy vs. 11.5 Gy (p=0.0018) to skin, 11.4 Gy vs. 9.6 Gy (p=0.0272)  
138 to ipsilateral lung and 18.5 Gy vs. 12.3 Gy (p=0.0013) to ribs, while D<sub>0.1</sub> to heart for left sided

139 lesions was lower, 3.0 Gy vs. 3.2 Gy ( $p=0.0476$ ), respectively. The detailed results can be found  
140 in Table 1.

## 141 **Discussion**

142 The debate on the advantages and disadvantages of different treatment techniques of  
143 APBI seems to be ongoing and refreshing when a new treatment modality appears. In spite of  
144 that several dosimetric and clinical comparative studies exist in the literature, no detailed  
145 analysis of the two most technologically advanced techniques, stereotactic CK and  
146 multicatheter HDR BT was performed yet.

147 In our previous study we have pointed out that the 3D-CRT provides the best heart  
148 protection compared to step and shoot and sliding window IMRT and IMAT [8]. However, the  
149 sliding window IMRT technique achieved the best plan quality index and should be  
150 recommended for APBI. Goggin et al. [27] found that CK and 3D-CRT plans resulted in similar  
151 tumour coverage and dose to critical structures, with the exception of the lung V5%, which was  
152 significantly smaller for 3D-CRT than CK-Iris and CK-multi-leaf: 6.2% vs. 39.4% and 17.9%.  
153 Both CK plans demonstrated lower ipsilateral breast V50% (25.5% and 24.2%, respectively)  
154 than the 3D-CRT (56.2%). The CK plans were more conformal but less homogeneous. In the  
155 comparison of Xu et al [28] the PTV coverage from CK plans was the highest and the ratio of  
156 V20% to V100% of the breast was the smallest. The heart and lung doses were similar in CK,  
157 IMRT and 3D-CRT plans, except for the V5% of the lung and the heart, which was higher in  
158 CK plans. Rault et al. [29] found insignificant dosimetric differences between CK, 3D-CRT  
159 and IMRT plans regarding the PTV coverage and sparing the lung and heart. However, CK  
160 reduced high doses of the non-target breast. Bonfantini et al. [30] concluded that CK and IMAT  
161 provided higher conformity than 3D-CRT plans, although reduced the dose to the OARs. CK  
162 resulted in longer treatment times, but with it the delivery accuracy is expected to be better than  
163 with IMAT and 3D-CRT techniques.

164 Khan et al. [31] stated that the dose coverage of the PTV was the highest with  
165 MammoSite balloon BT and the lowest using the 3D-CRT technique. Regarding sparing the  
166 ipsilateral breast, there were the same order between the studied techniques, but the mean dose  
167 of the ipsilateral lung was the lowest for IMRT and the highest for 3D-CRT, while in regard to  
168 volume of the heart irradiated by 5 Gy, IMRT yielded the lowest and MammoSite balloon  
169 resulted the highest value. The conflicting results published by different institutions most likely  
170 can be explained by differences in planning methods and the lack of standardized dosimetric  
171 parameters.

172 In our previous study it was shown that multicatheter HDR BT provided better sparing  
173 of normal tissue and OARs compared to IMRT [32]. Ipsilateral lung was spared better with BT,  
174 the mean lung dose was 5.1% vs. 7.1%, D1 was 39.0% vs. 54.3% and V5 was 32.9% vs. 41.7%  
175 in favour of BT. For left sided lesions the heart was generally irradiated by larger doses with  
176 BT. Mean heart dose was 4.5% vs. 2.0% and D2 was 18.3% vs. 19.7%, correspondingly.  
177 Volumetric maximal skin doses were similar, but regarding dose to 0.1 cm<sup>3</sup> and 1 cm<sup>3</sup> of most  
178 exposed volume, BT provided significantly less doses (76.6% vs. 94.4% and 60.2% vs. 87.8%,  
179 respectively). Ribs received less dose with BT with values of 45.6% vs. 69.3% for D1 and 1.4  
180 cm<sup>3</sup> vs. 4.2 cm<sup>3</sup> for V50. Dose to contralateral breast and lung was low with both techniques.  
181 No significant differences were observed in maximal doses, but dose to volumes of 0.1 cm<sup>3</sup> and  
182 1 cm<sup>3</sup> were less with BT for both organs. D1 was 3.2% vs. 6.7% for contralateral breast and  
183 3.7% vs. 5.6% for lung with BT and IMRT, respectively. In current study, we concluded the  
184 same result in term of stereotactic CK and HDR BT. However, the EQD2 total dose of the PTV  
185 was significantly lower with CK than with BT, D90 was 44.7 Gy and 49.0 Gy, BT yielded  
186 better sparing of OARs, except for the heart. V50 of the non-target breast was 10.5% and 3.3%,  
187 D1 to skin, ipsilateral lung and ribs were 35.2 Gy vs. 13.7 Gy, 14.0 Gy vs. 10.4 Gy and 28.7 Gy  
188 vs. 15.7 Gy, while D<sub>0.1</sub> to heart was 2.4 Gy vs. 3.6 Gy for left-sided lesions in our CK and BT  
189 plans. Only, between doses of the contralateral breast and contralateral lung for the two  
190 techniques there was no significant difference, D<sub>1</sub> was 0.3 Gy and 0.2 Gy to the contralateral  
191 breast and 0.5 Gy and 0.5 Gy to contralateral lung, respectively.

192 Based on the radiobiological evaluation of Hoekstra et al. [33] about multicatheter HDR  
193 BT, 3D-CRT, CK, IMAT and WBI, WBI resulted in the highest risk with 4.3% excess risk of  
194 secondary cancer for patients at age 50 years. Lung cancers accounted for 75-97% of secondary  
195 malignancies. For a typical early stage patient irradiated at 50 years, the excess risks of  
196 secondary lung cancer were 1.1% for HDR BT, between 2.2% and 2.5% for 3D-CRT or CK,  
197 3.5% for IMAT APBI and 3.8% for WBI. This is in good agreement with our dosimetric results,  
198 where BT resulted in lower dose to lung than CK therapy.

199 It has to be mentioned, that in our study BT plans were made on the planning CT of the  
200 CK without template and real catheters, and the breast was not compressed. So this anatomy  
201 was disadvantageous for BT. On the other hand, the virtual needles were not parallel but we  
202 tried to mimic their real trajectories. In the light of our results multicatheter HDR BT proved to  
203 be the optimal choice in APBI in the aspects of sparing most of the OARs beside dose coverage  
204 of the PTV. Stereotactic CK therapy resulted in higher dose to the OARs at the equivalent

205 prescribed dose to the PTV. And even, our study comparing the dosimetrical parameters of  
206 plans treated by CK and HDR BT using two separate patient cohorts is in progress.

## 207 **Conclusions**

208 Using interstitial multicatheter HDR brachytherapy, D90 dose of the PTV is higher than with  
209 stereotactic CyberKnife radiotherapy, however CK technique results more conformal dose  
210 distributions. Dose to skin, ipsilateral lung and ribs is higher, while dose to heart is lower with  
211 CK than with HDR BT technique. There is no difference in the dose of the contralateral breast  
212 and -lung. Overall, multicatheter HDR brachytherapy yields more advantageous treatment  
213 plans in accelerated partial breast irradiation, except for the dose conformality and the dose to  
214 heart, where CK plans are more optimal.

### 215 *Contributions:*

216 GF: worked out the concept, did the analysis and wrote this paper.

217 NM: made the contouring and discussed the details of this study.

218 VS: made the contouring and discussed the details of this study.

219 GS: performed the treatment plans of the CK and discussed the details of this study.

220 AH: discussed the details.

221 CsP: supported the study, revised the manuscript.

222 TM: supported the study, discussed the details and helped composing the manuscript.



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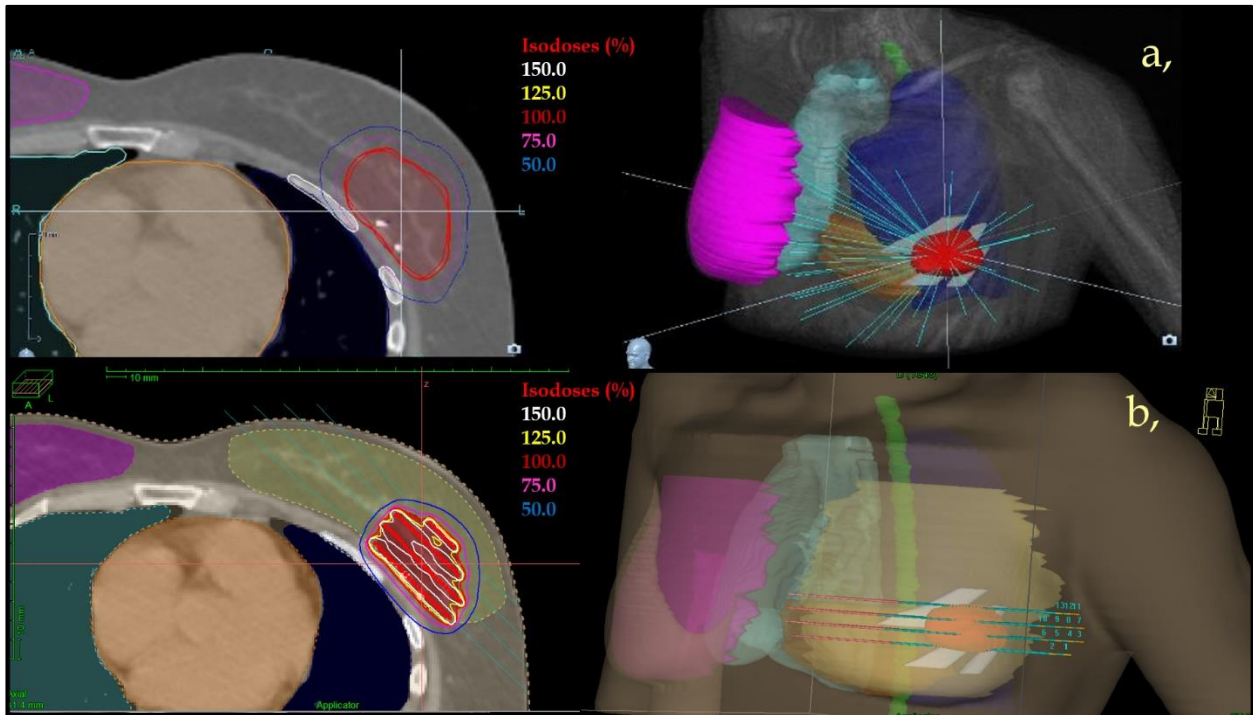
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	<b>CK</b>	<b>BT</b>	<b>p*</b>
<b>D90</b>	25.7 Gy (25.3-26.0) 102.7% (101.3-105.2)	27.0 Gy (26.7-27.9) 108.1% (107.0-111.6)	<b>&lt;0.001</b>
<b>COIN</b>	0.87 (0.77-0.92)	0.81 (0.77-0.85)	<b>0.0030</b>
<b>V50(non-target breast)</b>	10.5% (5.0-17.0)	3.3% (0.9-8.1)	<b>0.0010</b>
<b>D1(contralat breast)</b>	0.5 Gy (0.1-1.5) 2.2% (0.4-6.1)	0.4 Gy (0.0-2.3) 1.6% (0.0-9.3)	0.3112
<b>D0.1(contralat breast)</b>	0.9 Gy (0.1-3.9) 3.8% (0.3-15.5)	0.6 Gy (0.0-2.9) 2.5% (0.0-11.6)	0.1205
<b>D1(skin)</b>	20.6 Gy (9.0-26.5) 86.1% (52.4-106.0)	11.5 Gy (5.2-21.5) 46.1% (20.9-86.0)	<b>0.0018</b>
<b>D0.1(skin)</b>	23.7 Gy (9.8-28.7) 99.6% (70.2-114.6)	15.2 Gy (8.4-27.3) 60.9% (33.6-109.3)	<b>0.0203</b>
<b>D1(ipsilat lung)</b>	11.4 Gy (0.9-16.9) 45.0% (3.6-67.6)	9.6 Gy (6.4-12.8) 38.4% (25.6-51.2)	<b>0.0272</b>
<b>D0.1(ipsilat lung)</b>	14.4 Gy (8.6-20.0) 57.5% (34.2-80.0)	10.9 Gy (7.6-14.5) 43.8% (30.2-58.1)	<b>0.0008</b>
<b>D1(contralat lung)</b>	0.7 Gy (0.1-2.5) 2.9% (0.5-10.0)	0.7 Gy (0.2-1.7) 2.9% (0.8-6.8)	0.5345
<b>D0.1(contralat lung)</b>	0.9 Gy (0.3-2.8) 3.7% (1.3-11.2)	1.0 Gy (0.4-2.1) 4.0% (1.6-8.4)	0.4671
<b>D1(heart)</b>	2.7 Gy (0.8-8.0) 10.5% (3.2-32.0)	2.8 Gy (0.1-5.7) 11.2% (0.4-22.8)	0.0534
<b>D0.1(heart)</b>	3.0 Gy (1.6-8.2) 12.1% (6.4-32.8)	3.2 Gy (0.1-8.5) 12.8% (0.4-34.0)	<b>0.0476</b>
<b>D1(ribs)</b>	18.5 Gy (10.9-24.7) 73.6% (43.5-98.8)	12.3 Gy (8.7-16.3) 49.0% (34.9-65.1)	<b>0.0013</b>
<b>D0.1(ribs)</b>	23.3 Gy (14.8-27.7) 93.2% (59.3-110.6)	15.3 Gy (9.9-20.3) 61.2% (39.5-81.4)	<b>0.0012</b>

333 **Table 1. Mean total doses of CyberKnife (CK) and high-dose-rate brachytherapy (BT) of**  
334 **breast cancer. D90: the minimum dose delivered to 90% of the planning target volume,**  
335 **COIN: conformal index, V50(non-target breast): the relative volume of non-target breast**  
336 **receiving at least the 50% of the prescribed dose, D<sub>1</sub>(x) and D<sub>0.1</sub>(x): the minimal dose of**  
337 **the most exposed 1 and 0.1 cm<sup>3</sup> of ‘x’ organ at risk, where x are contralateral breast**  
338 **(contralat breast), skin, ipsilateral lung (ipsilat lung), contralateral lung (contralat lung),**  
339 **heart and ribs. \*Wilcoxon Matched Pairs Test.**

340

341 **Figures:**



342

343 **Figure 1. Axial CT slide (left) and 3D reconstruction (right) of a stereotactic CyberKnife**  
344 **breast radiotherapy (a,) and a multicatheter interstitial high-dose-rate breast**  
345 **brachytherapy (b,) plan. PTV: red, ipsilateral breast: yellow, contralateral breast: pink,**  
346 **spinal cord: green, ribs: white, heart: orange, ipsilateral lung: dark blue, contralateral**  
347 **lung: light blue.**