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Phase III randomised trial

Cost of prostate image-guided radiation therapy: Results of a randomized trial

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ABSTRACT

Purpose: This cost analysis aimed to quantify the cost of IGRT in relation to IGRT frequency and modality with Cone Beam Computed Tomography (CBCT) or orthogonal electronic portal imaging with fiducial markers (EPI-FM).

Material and methods: Patients undergoing IGRT for localized prostate cancer were randomized into two prostate control frequencies (daily or weekly). Costs were calculated based on the micro-costing results according to hospitals' perspectives (in Euros, 2009) and the time horizon was radiation therapy.

Results: A total of 208 patients were enrolled in seven French cancer centers. A total of 6865 fractions were individually analyzed. The mean total treatment fraction duration was 21.0 min for daily CBCT and 18.3 min for daily EPI-FM. Increasing the control frequency from weekly to daily increased the mean treatment fraction duration by 7.3 min (+53%) for CBCT and 1.7 min (+10%) for EPI-FM ($p \leqslant 0.01$). The mean additional cost per patient of daily controls compared with weekly controls was €679 and €187 for CBCT and EPI-FM, respectively ($p < 0.0001$).

Conclusions: The incremental costs due to different prostate IGRT strategies are relatively moderate, suggesting that daily IGRT combined with intensity-modulated RT (IMRT) could be administered in cases of high-dose radiation delivery to the prostate.

Accurate prostate localization is critical in prostate cancer radiotherapy, particularly for highly conformal techniques such as intensity-modulated radiotherapy (IMRT), which deliver high doses of radiation to the prostate. Intra-pelvic prostate motion can reach up to 2 cm along the anteroposterior axes, mainly due to rectal volume variations, while planning target volume (PTV) margins are commonly less or equal to 1 cm. Rectal distension on planning computed tomography (CT) has consequently been shown to increase the risk of recurrence [1,2].

In the "standard historical" setting, electronic portal imaging (EPI) without fiducial markers only corrects for patient position. Image-guided radiotherapy (IGRT) has therefore been gradually developed in order to correct for prostate localization. The two main prostate IGRT modalities currently used are orthogonal imaging (EPI or kilovoltage) combined with intra-prostatic fiducial markers and cone beam CT (CBCT). Cost studies, although limited in number, suggest that IGRT is particularly costly, mainly because of the increase in treatment fraction duration, although this is dependent on IGRT modality [3,4]. In addition, the optimal positioning control frequency has not yet been clearly established, which also potentially affects the cost of IGRT [3]. Daily controls correct for both systematic and random prostate displacements. Day 1, 2, 3, and weekly controls (which define the average prostate position during treatment) only correct for systematic prostate displacements. The dosimetrical consequences of systematic and random geometrical uncertainties differ, with the deteriorating effects of random variations being much smaller than those caused by systematic deviation [5,6].

Therefore, we designed a randomized study that aimed to compare daily controls with weekly controls in prostate cancer IGRT, in terms of both clinical outcome and cost. This paper presents the cost analysis of the two IGRT frequency strategies, in relation to IGRT modality (CBCT or fiducials) in several French cancer centers.

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Materials and methods

Study population

The inclusion criteria were patients with localized prostate adenocarcinoma, N0 or N−, without metastasis assessed by abdominopelvic CT and bone scan. Patients had to undergo 3D conformal radiotherapy, with or without IMRT, and with or without androgen deprivation, depending on risk group. The total dose could range from 70 Gy to 80 Gy in the prostate and could reach 46 Gy in the seminal vesicles. The dose per fraction was 2 Gy. Target delineation and dose distribution had to respect the French Study Group on Urogenital Tumors guidelines [7]. The PTV margins were defined as 1 cm all around the prostate and the seminal vesicles except in the posterior direction where the margin was only 5 mm. All patients provided informed consent. Exclusion criteria were patients with hip prostheses, pacemakers and target volume including the pelvic lymph nodes.

Study design and IGRT procedure

The cost analysis was performed prospectively in a multicenter randomized phase III trial within the framework of the French National Cancer Institute (INCa). Patients were randomized into two prostate IGRT control frequency groups: daily control or weekly control (day 1, day 2, day 3, then weekly, with average prostate positioning on the days when prostate position was not controlled). IGRT modalities consisted of CBCT or fiducials visualized using orthogonal EPI, depending on center practice. A radiation oncologist was required to approve patient position for CBCT but not for EPI with fiducials. Patients with protocol deviations were excluded from the study. Deviations were defined as more than three fractions without prostate positioning control in the daily setting arm, and more than five supplementary fractions with prostate positioning control in the weekly setting arm.

Cost assessment

Economic analysis was performed from the perspective of each hospital during the trial. Data on consumption of resources were prospectively collected from the beginning of the first irradiation fraction, until the end of the last fraction. Calculations were strictly based on a micro-costing approach [8]. Only resources that entered the hospital production process and which were likely to vary between the strategies being compared were considered. Case report forms were used to collect resource utilization data for all irradiation fractions, and when appropriate, for the implementation of fiducial markers. Unit prices and costs were provided by the accounting departments of the centers participating in the study. All costs were expressed in €, and all taxes included. The time required from staff and the duration of irradiation and operating room occupation (for fiducials) were assessed for each patient by direct measurement using chronometers. The mean yearly wage costs were calculated based on what a staff member would earn after 10 years of professional experience. The linear lifetime period for the linear accelerator was 12 years. As the future number and types of upgrades they will receive remain uncertain, an estimation of stationary conditions over a period of 12 years was made. The annual operating time of the linear accelerator was estimated (from questionnaires) to amount to 2600 h, corresponding to 52 weeks per year, 5 days per week, and 10 h per day (ranging from 7.5 h to 12.5 h). The time per year required for internal maintenance and quality control of the accelerator by the physicist was estimated to amount to 392 h with CBCT and 357 h without CBCT. Time per year for the medical technician was 64 h with CBCT and zero without CBCT. The linear lifetime period of the software was five years. The unit costs of the operating room, including consumables and clinical infrastructure (equipment), were obtained from the accounting departments of the participating centers. All formulae are shown in Table 1.

It must be noted that the aim of the present study was not to estimate the overall cost of radiotherapy. Thus, only factors that potentially affected IGRT cost were selected. Incremental costs were finally calculated between daily and weekly positioning frequency for IGRT, with CBCT or fiducial markers.

Statistical analysis

The number of patients intended to be included in the cost analysis was 200. Based on unpublished pilot work, 50 patients per arm were considered sufficient to ensure a significant difference between costs with a statistical power of 80%. Patient and disease characteristics, along with resource consumption and costs, were summarized using descriptive statistics. Univariate differences between the study arms were determined using Pearson's chi-squared or Fisher's exact test for categorical variables, and the Wilcoxon–Mann–Whitney test for continuous variables. Multiple linear regressions were performed to model the relationship between the total cost and potentially explanatory variables (IGRT frequency and modality, use of IMRT, age, WHO performance, Gleason score, prostate-specific antigen (PSA), TNM stage, D'Amico risk classification, androgen deprivation, total radiation dose, and hospital status). The mean cost sensitivities of the different IGRT strategies (CBCT or fiducial markers, with daily or weekly imaging) to variations in resources consumption and unit cost parameters were assessed independently. Variations of ±10% in the value of each parameter were retained and illustrated graphically within Tornado diagrams [9]. Uncertainties regarding costs were also assessed by probabilistic analysis using non-parametric bootstrap methods: 1000 simulated bootstrap samples were generated by independent draws for CBCT or fiducial markers, with daily or weekly imaging. All 95% confidence intervals were computed. All analyses were performed using SAS® v.9.1 (SAS Institute, Cary, NC), STATA® v.11.0 and Treeplan SensIt®.

Results

Patients and treatment characteristics

Between January 2007 and May 2012, 420 patients were included in this randomized trial comparing the two IGRT control frequencies with clinical outcome evaluation as the main endpoint. The first 208 patients were enrolled for the cost-analysis from January 2007 to May 2011 in five French cancer centers located within academic institutions (Léon Bérard (Lyon), René Gauducheau (Nantes), Jean Godinot (Reims), Eugène Marquis (Rennes), Henri Mondor (Créteil)) and two private radiation centers (Sainte Catherine (Avignon) and Pont de Chaume (Montauban)). Twenty-five patients were excluded from analysis due to protocol deviation as previously described. Among the 183 analyzed patients, 93 patients had daily control and 90 patients had weekly control. CBCT was used for 128 patients and fiducial markers for 55 patients. A total of 6865 fractions were individually analyzed (4772 fractions with CBCT and 2093 with fiducial markers). Patient, tumor and treatment arm data are presented in Table 2. These characteristics were not statistically different between the two randomized arms, except for the total number of fractions and the radiotherapy technique in the case of CBCT.

Resource consumption

Table 3 illustrates the time spent by staff and treatment room occupation duration per irradiation fraction according to IGRT