Radiation-Related Cancer Risk Associated With Surveillance Imaging for Metastasis From Choroidal Melanoma

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Objective: To estimate the lifetime attributable risk of cancer associated with whole-body positron emission tomography (PET)/computed tomography (CT) and with CT of the chest, abdomen, and pelvis if performed at various frequencies and for different durations for surveillance of patients with primary choroidal or ciliary body melanoma for distant metastasis.

Methods: Effective radiation doses for whole-body CT and for CT of the chest, abdomen, and pelvis were calculated using Monte Carlo simulation studies. The effective dose of the PET scan was estimated by multiplying fludeoxyglucose F18 radioactivity with dose coefficients. Lifetime attributable risks of cancer were calculated using the approach described in the Biological Effects of Ionizing Radiation VII report.

Results: For a 50-year-old patient, an annual CT of the chest, abdomen, and pelvis for 10 years carries an estimated lifetime attributable risk of cancer of 0.9% for male patients and 1.3% for female patients, whereas an annual PET/CT each year for 10 years carries an estimated lifetime attributable risk of cancer of 1.6% for male patients and 1.9% for female patients. Lifetime risk was found to be higher in younger, female patients. The lifetime attributable risk of cancer was estimated to be as high as 7.9% for a 20-year-old female patient receiving a PET/CT scan every 6 months for 10 years.

Conclusions: Aggressive surveillance protocols incorporating CT scanning or PET/CT scanning for detection of metastasis from primary choroidal or ciliary body melanoma appear to confer a significant substantial risk of a secondary malignant tumor in patients who do not succumb to metastatic melanoma within the first few post-treatment years.

radiation exposure. These cancer risks can be estimated using data on cancer incidence and mortality in atomic bomb survivors as well as from medical and occupational radiation studies.12 The Biological Effects of Ionizing Radiation VII (BEIR VII) report comprehensively reviewed the biologic and epidemiologic data related to health risks from ionizing radiation exposure.12,13 The effective dose of ionizing radiation is measured in sieverts (Sv), which is the product of the amount of radiation absorbed by the tissue multiplied by a tissue weighting factor (sensitivity of the tissue to radiation) multiplied by a radiation weighting factor (type of radiation). Sieverts are a quantitative measure of the biologic effects of ionizing radiation, rather than just the absorbed dose (measured in grays [Gy]). Radiation exposures from various sources such as background radiation and medical radiation are typically reported in millisieverts.14 For low-dose exposures such as background radiation and medical radiation are measured in grays (Gy). Radiation exposures from various sources such as background radiation and medical radiation are typically reported in millisieverts.14 For low-dose exposures (doses <100 mSv), the BEIR VII report supported a linear no-threshold model, whereby the risk for cancer induction decreases linearly with decreasing radiation dose.13 Using the BEIR VII report, we can estimate the lifetime attributable risk (LAR) for cancer associated with various radiation dosages. This method has been widely used to estimate the LAR of cancer following a number of different studies, including those using CT/ coronary angiography, mammography, CT of the chest, CT of the abdomen, whole-body CT, and whole-body PET/CT.15-20

The purpose of our study was to estimate the LAR of cancer in patients receiving various surveillance imaging protocols for metastatic disease following a diagnosis of primary choroidal melanoma. The following surveillance protocols were included in our study: annual or biannual whole-body PET/CT; annual or biannual CT of the chest, abdomen, and pelvis or biannual alternating whole-body PET/CT; and CT of the chest, abdomen, and pelvis. The risks of cancer were calculated for men and women who underwent one of the prior imaging studies and who underwent one of these surveillance protocols for 5 or 10 years.

METHODS

The ionizing radiation dose for each type of imaging study was estimated, and the cancer risk was then calculated using data from the BEIR VII report.

ESTIMATING RADIATION DOSES OF CT STUDIES

In the NRPB-SR250 report,11 published by the National Radiation Protection Board (NRPB), Monte Carlo simulations utilizing an anthropomorphic mathematical phantom were used to calculate the radiation doses to individual organs during a CT scan. The ImPACT CT Patient Dosimetry Calculator (London, England [http://www.impactsan.org]) is a software tool that incorporates this original NRPB data set and also accounts for variation in the scanning equipment. To estimate the effective dose for a whole-body CT, a 70-kg person was modeled using a 64-slice scanner (SOMTOM Sensation 64; Siemens AG) with the following scan parameters: 120 kV, 300 mA, 0.984 pitch, 1.2-mm collimation, and a scan range from 5 to 94 cm. Calculations were then repeated with a scan range from 5 to 69.5 cm representative of a CT of the chest, abdomen, and pelvis.

ESTIMATING RADIATION DOSES OF PET

Whole-body fluorodeoxyglucose F18 (FDG)–PET scanning was performed after the injection of 370 MBq of FDG. The PET images were acquired at approximately 10 stations per patient with an acquisition time of 4 minutes per station, from the top of the head to the feet. The organ doses were calculated by multiplying the FDG activity by the organ-specific coefficient recommended in publication 80 from the International Commission on Radiological Protection.21 The total body dose was obtained by summing individual organ-effective doses multiplied by the tissue weighting factors given in publication 60 from the International Commission on Radiological Protection.22

RISK CALCULATIONS USING THE BEIR VII REPORT

Table 12D-1 of the BEIR VII report summarizes the LAR of cancer resulting from a 100-mSv organ dose equivalent based on sex, age at exposure, and organ.13 For patients without available data on age, a linear interpolation between the 2 nearest ages was used to estimate the LAR. The LAR for the theoretical 100-mSv organ dose was scaled linearly based on the calculated organ dose from the Monte Carlo simulations. For example, the LAR of breast cancer in a 40-year-old woman following a 100-mSv breast dose is 141 per 100 000 per Table 12D-1 of the BEIR VII report. For our dosimetry model, a CT of the chest, abdomen, and pelvis leads to a 20-mSv equivalent dose to the breast. The LAR of breast cancer from this 20-mSv dose is therefore (20/100) × (141/100 000) or 0.03%.

For PET/CT studies, the whole-body LAR of cancer was calculated by using the data available for all cancers in Table 12D-1 of the BEIR VII report. For studies of CT of the chest, abdomen, and pelvis, the whole-body LAR of cancer was estimated by summing site-specific LARs for irradiated organs. Depending on the protocol (annual vs biannual), the LAR for each study at each age was calculated. Per the BEIR VII model, the overall LAR of cancer for each protocol was estimated by summing all of the LARs for each age during the surveillance time period. This analysis was repeated for both male and female patients 20 to 70 years of age with the different surveillance protocols. Risk calculations were performed using Excel 2008 (Microsoft Corp). Our Figure was plotted in R version 2.13.0 using ggplot2.

RESULTS

Our Table summarizes the estimated organ-specific effective doses of radiation following whole-body CT vs CT of the chest, abdomen, and pelvis. Total effective doses were also calculated based on tissue weighting factors published by the International Commission on Radiological Protection.22 The total effective dose following whole-body CT was found to be 22.8 mSv in men and 22.0 mSv in women. The total effective dose of a CT of the chest, abdomen, and pelvis was found to be 20.35 mSv in men and 19.85 mSv in women. The estimated effective dose of FDG with an activity of 370 MBq was found to be 7.0 mSv. Therefore, the total effective dose of whole-body PET/CT was calculated to be 29.8 mSv in men and 29.0 mSv in women.
The LAR of cancer following a single whole-body PET/CT was found to be 0.29% (1 in 344) and 0.48% (1 in 208) for men and women, respectively, who were 20 years of age compared with 0.10% (1 in 1000) and 0.12% (1 in 833) for men and women, respectively, who were 70 years of age. The LAR of cancer following a single CT of the chest, abdomen, and pelvis was found to be 0.17% (1 in 588) and 0.30% (1 in 333) for men and women.
respectively, who were 20 years of age compared with 0.06% (1 in 1667) and 0.08% (1 in 1250) for men and women, respectively, who were 70 years of age.

Our Figure, A, shows the LAR of cancer in men who underwent the annual or biannual whole-body PET/CT protocol, the annual or biannual CT of the chest, abdomen, and pelvis protocol, or an alternating protocol, which was continued for 5 years. The risks of cancer following a single whole-body PET/CT or a single CT of the chest, abdomen, and pelvis are shown for comparison. Our Figure, B, shows the LAR of cancer in men for the same protocols continued for 10 years. The most aggressive surveillance protocol (a PET/CT scan every 6 months for 10 years) has an LAR of cancer of 5.0% (1 in 20) for a 20-year-old man compared with 1.6% (1 in 63) for a 70-year-old man.

Similarly, our Figure, C and D, demonstrates the LAR of cancer for women using the same protocols, continued for 5 and 10 years, respectively. The most aggressive surveillance protocol (a PET/CT scan every 6 months for 10 years) has an LAR of cancer of 7.9% (1 in 13) for a 20-year-old woman compared with 1.8% (1 in 56) for a 70-year-old woman.

For a 50-year-old patient, an annual PET/CT each year for 5 years carries an LAR of cancer of 0.85% (1 in 118) for men and 1.0% (1 in 100) for women. This risk increases to 1.6% (1 in 63) and 1.9% (1 in 53) for men and women, respectively, if this annual protocol is continued for 10 years. If the frequency of surveillance is increased to every 6 months and continued for 10 years, then the LAR further increases to 3.2% (1 in 31) and 3.9% (1 in 26) for men and women, respectively. An annual CT of the chest, abdomen, and pelvis for 10 years for a 50-year-old patient carries an LAR of cancer of 0.9% (1 in 111) for men and 1.3% (1 in 77) for women. This risk increases to 1.8% (1 in 56) for men and 2.5% (1 in 40) for women if the frequency of surveillance is increased to every 6 months.

**COMMENT**

Surveillance for metastasis from choroidal melanoma requires consideration of radiation-related LAR, surveillance without radiation, the relative risk of metastasis, and the potential benefits of early detection of metastasis. Our study demonstrates that the LAR of cancer varies by age and sex, with younger female patients being more radiosensitive. This is consistent with other studies that report increased radiosensitivity of organs such as the breast or thyroid in younger patients. As expected based on the estimated radiation dose of each study, the LAR of cancer related to PET/CT protocols is higher than that related to CT of the chest, abdomen, and pelvis, with an alternating protocol carrying an intermediate LAR of cancer.

Our estimates for radiation doses are consistent with other published reports that use alternative methods to estimate radiation doses. In a study investigating the radiation exposure of patients undergoing whole-body PET/CT scans at 4 different hospitals, Alderson RANDO phantoms (Alderson Research Laboratories Inc) equipped with thermoluminescent dosimeters were used. Effective doses for a whole-body PET/CT scan were estimated to range from 23.7 to 26.4 mSv. Another study that also used Alderson RANDO phantoms estimated an effective dose of 31.91 mSv for women and 32.18 mSv for men following a whole-body PET/CT scan.

The LAR calculations are based on strict annual or biannual protocols continued for a full 5 or 10 years. The realities of a patient’s compliance and a clinician’s willingness to adhere to such a protocol mean that most patients likely receive fewer total imaging studies than modeled in our study and, therefore, have a lower LAR of cancer than calculated in our study. Conversely, our study does not include data on radiation exposure from studies that a patient may have received for other medical conditions. For example, a patient with coronary artery disease in addition to a choroidal melanoma may undergo a CT coronary angiography, which would confer additional radiation exposure. In this situation, the LAR of cancer would be greater than what was estimated in our study.

Of note, the BEIR VII risk estimates were developed for patients with typical life expectancies for age and sex. With the significant mortality of choroidal melanoma, fatal in about 50% of cases, and the reported lag time between radiation exposure and the radiation-related development of cancer, it is likely that many patients will not survive long enough to develop these complications. However, a recent model for survival following treatment of choroidal melanoma suggests that, while, on average, there is a 50% mortality rate, on an individual basis, patients either have a considerably better or worse prognosis, based primarily on whole chromosome 3 loss in the tumor (monosomy 3) and other factors. Furthermore, a recent retrospective study found that younger patients (defined as <20 years of age) were significantly less likely to develop metastatic disease compared with older patients (>60 years of age). Our results, along with the patient’s age and survival probability, can be considered when discussing the option of surveillance. For a young patient with an excellent survival probability and low risk for metastatic disease, the LAR of cancer from an aggressive PET/CT surveillance protocol may outweigh the benefits. For an older individual with a poor prognosis and high risk for metastatic disease, an aggressive protocol may have the benefits of detecting metastases earlier and enabling initiation of treatment or enrollment in a treatment trial sooner, which may outweigh the risks.

There is wide variability in the type and frequency of surveillance being implemented for metastasis. Among the imaging modalities of magnetic resonance imaging (MRI), CT, PET, and PET/CT, the optimal surveillance protocol has yet to be determined. The reported sensitivities of PET or PET/CT in the detection of metastatic disease have been conflicting. In a recent study of 10 patients with biopsy-proven hepatic metastases found that MRI was better at detecting small hepatic metastases than PET/CT. This begs the question of whether serial MRIs could be used for surveillance, therefore eliminating the risks of radiation exposure entirely. Although MRI scans may be better at identifying concern-
ing lesions, its ability to differentiate between a benign lesion and a malignant lesion may be more limited.\(^1\) Furthermore, MRI scans are limited by a patient’s body habitus and a patient’s claustrophobia and are contraindicated for patients with metallic implants. However, for a patient who can tolerate an MRI scan, a combination of MRI and PET/CT scans may be a better way to minimize radiation exposure while maintaining a high degree of sensitivity and specificity. For a young patient, one could consider monitoring serial MRI scans for surveillance and using PET/CT scans to better characterize abnormal lesions detected by MRI.

The BEIR VII risk model has been used in a number of different radiologic studies\(^5\) to estimate cancer risk. However, there are a few limitations to using this model. Risk estimates have yet to be verified by long-term epidemiologic studies. The BEIR VII risk model is based on the controversial assumption that there is a linear, no-threshold relationship between radiation dose and cancer risk. Although a minority of organizations feel that this assumption may overestimate or underestimate risks, the majority conclude that it best fits the data and should remain the standard.\(^1,\)\(^2\)

Our study only represents an estimate of increased LAR of cancer associated with periodic CT and/or PET/CT imaging. A substantial increase in the frequency of secondary cancers has yet to be reported for actual patients being treated for choroidal or ciliary body melanoma who receive such periodic imaging for detection of metastatic disease. Proof of these estimates would require a prospective or retrospective analysis of the incidence of nonmelanoma cancer in patients with comparable metastatic risk (based on clinical, histopathologic, and cytogenetic prognostic factors) who survived for 10 or more years without metastatic disease following treatment of the primary tumor and who underwent (1) no surveillance or only radiation-sparing surveillance or (2) one of the surveillance protocols modeled in our study. If frequent CT and/or PET/CT imaging truly induces secondary cancers, then a higher incidence of nonmelanoma cancer would be expected in the latter group.

Currently, there is little evidence demonstrating a survival benefit from any of the existing treatments of metastasis from choroidal melanoma.\(^4\) Furthermore, no surveillance testing regimen or frequency has been proven to increase survival.\(^3\) However, there is always the hope that this will change once an effective treatment of metastasis is developed. At this time, the detection of early metastatic disease may allow patients to enroll in treatment studies before the onset of end-stage disease, therefore assisting in the development of new therapies.

Aggressive surveillance protocols that entail CT scanning or PET/CT scanning for the monitoring of patients with primary choroidal or ciliary body melanoma for distant metastasis appear, on the basis of our study, to confer a significant substantial risk of secondary malignant tumors from exposure to ionizing radiation. With limited treatment options for metastatic disease, a discussion of the risks and benefits of the various surveillance methods must take place with patients during the course of their management. It is important to consider a patient’s age, sex, and disease prognosis when establishing a surveillance protocol to minimize the long-term risks of radiation-related secondary malignant tumors. For a young patient with an excellent probability of survival and at low risk for metastatic disease, the LAR of cancer from an aggressive PET/CT surveillance protocol may outweigh the benefits. In this population, serial MRI studies may be a safer option, with PET/CT studies obtained only as needed to better characterize abnormal lesions.

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