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Original Citation:

Availability:
This version is available at: 11577/3299685 since: 2019-05-03T17:33:08Z

Publisher:
Editor-in-Chief: Jeffrey F. Williamson | Washington University | Radiation Oncology

Published version:
DOI: 10.1002/mp.13393

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Internal radiation dose assessment after administration of radiopharmaceuticals prepared with cyclotron-produced $^{99m}$Tc

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Pre-print

Accepted for publication in Medical Physics:
ABSTRACT (500 words)

**Purpose:** $^{99m}$Tc is the radionuclide most widely used in diagnostic nuclear medicine. It is readily available from $^{99}$Mo/$^{99m}$Tc generators as a β-decay product of the $^{99}$Mo ($T_{1/2}$=66 h) parent nuclide. The latter is obtained as a fission product in nuclear reactors by neutron-induced reactions on highly enriched uranium. Alternative production routes, such as direct reactions using proton beams on specific target materials [e.g. $^{100}$Mo(p,2n)$^{99m}$Tc] are a reliable and relatively cost-effective method. However, the results of the LARAMED (Laboratory of Radionuclides for Medicine) project research from the Legnaro National Laboratories of the National Institute for Nuclear Physics (LNL-INFN), showed that the extracted $^{99m}$Tc from the proton-bombarded $^{100}$Mo-enriched target contains small quantities of several technetium radioisotopes ($^{93m}$Tc, $^{93}$Tc, $^{94}$Tc, $^{94m}$Tc, $^{95}$Tc, $^{95m}$Tc $^{96}$Tc and $^{97m}$Tc).

The aim of this work was to determine the patient dose increase (DI) due to the contribution of Tc-radioisotopes generated as impurities, after the administration of four radiopharmaceuticals prepared with cyclotron-produced $^{99m}$Tc (CP-$^{99m}$Tc).

**Methods:** Four $^{99m}$Tc-radiopharmaceuticals (pertechnetate, sestamibi, hexamethylpropylene-amine oxime (HMPAO) and disodium etidronate (HEDP)), were considered in this study. The biokinetic models reported by the International Commission on Radiological Protection (ICRP) for each radiopharmaceutical were used to determine the main source organs and to calculate the number of disintegrations that occurred in each source organ ($N_{source}$) for each Tc-radioisotope present in the CP-$^{99m}$Tc solution. Then, equivalent dose in the main organs and effective dose were calculated for each Tc-radioisotope with the OLINDA/EXM software versions 1.1 and 2.0, using the calculated $N_{source}$ and the adult male phantom as program inputs. Finally, the total effective dose produced by all Tc-radioisotopes present in the CP-$^{99m}$Tc solution was calculated at five different times after the end of bombardment (EOB), using $^{100}$Mo-enriched (i.e. 99.05 %) metallic target, and compared with the effective dose delivered by the generator-produced-$^{99m}$Tc.
Results: In all cases, the total effective DI of CP-99mTc-radiopharmaceuticals, calculated with both versions of the OLINDA software, remained within the 10% limit from 6 up to 12 h after EOB. 94mTc and 93mTc are the Tc-radionuclides with the highest concentration in the CP-99mTc solution at EOB. However, their contribution to DI 6 h after EOB is minimal, due to their short half-life. Although their concentration in the CP-99mTc solution is 5 times less than 94mTc and 93mTc at the EOB, the radioisotopes with the largest contribution to the effective DI are 96Tc, followed by 95Tc and 94Tc, due to the type of their emissions and relatively long half-life.

Conclusion: The increase in the patient radiation dose caused by the other technetium-nuclides contained in CP-99mTc produced as described in this paper, is quite low. Therefore, it was concluded that although in the CP-99mTc solution the concentrations of two radionuclides, 94Tc and 95Tc, are outside the limits established by the European Pharmacopoeia, it could be used in routine nuclear medicine diagnostic studies, but would have to be administered from 6 to 12 h after the EOB to maintain the effective DI within the 10 % limit.

Keywords: cyclotron-produced 99mTc, 99mTc-radiopharmaceuticals effective dose, Tc-dosimetry, Dose Increase (DI).
1. INTRODUCTION

Technetium-99m is the radionuclide most widely used in diagnostic nuclear medicine. Sodium pertechnetate is used as raw material to prepare more than twenty $^{99m}$Tc-radiopharmaceuticals employed for the detection of diverse physiological and pathological conditions such as myocardial perfusion, kidney and brain disorders as well as bone metastases. The radioisotope is readily available in hospitals from $^{99}$Mo/$^{99m}$Tc generators, as $\beta$-decay product of $^{99}$Mo, which in turn, is a selected and purified fission product of weapon-grade highly enriched uranium (HEU-WG), special targets in nuclear reactors. However, the majority of $^{99}$Mo isotope global production is the work of less than seven nuclear reactor facilities worldwide and most of them are close to being permanently shut down at the end of their running periods (more than 50 years of operation). Therefore, alternative production routes for both $^{99}$Mo and $^{99m}$Tc nuclides are currently being evaluated. Among them, the use of cyclotrons to produce either $^{99}$Mo or $^{99m}$Tc is one of the most interesting and promising approaches.

Experimental studies on $^{99m}$Tc production by cyclotrons were initiated within the framework of the TECHN_OSP/LARAMED (Laboratory of Radionuclides for Medicine) research project, by the Legnaro National Laboratories at the National Institute for Nuclear Physics, Italy (LNL-INFN). A PETtrace GE cyclotron was used to obtain cyclotron-produced $^{99m}$Tc (CP-$^{99m}$Tc), using the $^{100}$Mo(p,2n)$^{99m}$Tc reaction on $^{100}$Mo-enriched (i.e. 99.05 %) metallic targets, the isotopic composition of the enriched molybdenum used was a good compromise between enriched and cost.

$^{99m}$Tc was extracted and purified from the irradiated targets by solvent extraction through the Methyl-Ethyl Ketone (MEK) method, using a self-developed automated module with an efficiency greater than 90%.

Results demonstrated that the direct reaction method is reliable and a relatively cost-effective option to produce $^{99m}$Tc. However, gamma-ray spectrometry analyses of the obtained purified $^{99m}$Tc solutions demonstrated the presence of small quantities of several technetium radioisotopes, such as $^{93}$Tc, $^{93m}$Tc, $^{94}$Tc, $^{94m}$Tc, $^{95}$Tc, $^{95m}$Tc, $^{96}$Tc and $^{97m}$Tc. It has been reported by previous studies that the
The abundance of these contaminant nuclides is basically dependent on some changing factors, such as the target’s isotopic composition, beam energy level, target thickness, irradiation time and time span from irradiation to administration \(^{10,11}\). Despite the presence of technetium isotopes in the solution, all radiopharmaceuticals labelled with CP-\(^{99m}\)Tc showed no differences in the labelling efficiency, radiochemical purity and biological behaviour when compared to the radiopharmaceuticals labelled with generator-produced \(^{99m}\)Tc (GP-\(^{99m}\)Tc) \(^{12,13}\). It was also demonstrated that scatter-corrected images of rats, obtained after administration of radiopharmaceuticals for myocardial perfusion and bone imaging labelled with CP-\(^{99m}\)Tc and GP-\(^{99m}\)Tc, were comparable \(^{12,14}\). Selivanova et al confirmed these results demonstrating no difference in whole body biodistribution images of patients, after administration of sodium pertechnetate produced by cyclotron and generator \(^{15}\).

The main problem with the technetium impurities is that they contribute to the radiation dose of the patient \(^{10}\). Thus, the European Pharmacopoeia Commission established a monograph of sodium pertechnetate obtained by proton irradiation of highly-enriched molybdenum-100 targets, in order to set the limits of radionuclide impurities for the solutions used in clinical diagnosis \(^{16}\).

The aim of this work was to determine the increase of the total effective dose in patients due to the contribution of all Tc-radionuclides produced as impurities. Effective dose increase was calculated for four radiopharmaceuticals prepared with \(^{99m}\)Tc produced by a PETtrace GE cyclotron, evaluating five times points after the end of bombardment (EOB), in order to find the best period when the CP-\(^{99m}\)Tc radiopharmaceuticals could be used.

### 2. MATERIALS AND METHODS

Four of the \(^{99m}\)Tc-radiopharmaceuticals most used in the clinical diagnosis at the Nuclear Medicine Department of the Veneto Institute of Oncology IOV-IRCCS were considered for this study: sodium pertechnetate, used in clinical diagnosis of thyroid function and morphology; disodium etidronate (HEDP), a phosphonate commonly used for defining bone metastasis in cancer patients; hexamethylpropyleneamine oxime (HMPAO), used as a tracer of brain function and sestamibi
(MIBI), widely used in cardiac scans for diagnosis of heart disease. The total effective dose increases
were assessed considering the administration of the four radiopharmaceuticals labelled with both
GP-$^{99m}$Tc and CP-$^{99m}$Tc produced by the alternative $^{100}$Mo(p,2n) reaction route, through a GE
PETtrace cyclotron and using enriched ($99.05\%$) molybdenum-100 metallic targets.

2.1 Number of disintegrations in the source organs

The biokinetic models published by the International Commission on Radiological Protection
(ICRP) were used to determine the main source organs for each radiopharmaceutical. Pertechnetate
and HEDP biokinetic models were obtained from ICRP publication 53: “Radiation dose to patients
from radiopharmaceuticals”$^{17}$; HMPAO and MIBI models were obtained from publication 80
(addendum 2 to ICRP publication 53)$^{18}$. The cumulated activities, or number of disintegrations that
occurred in the source regions over time ($N_{\text{source}}$), were calculated for each radionuclide taking into
account the related biological elimination constant for each source organ reported by the ICRP
radiopharmaceutical models.

The number of disintegrations in the bladder ($N_b$) for each radionuclide was calculated for all 4
radiopharmaceuticals using the kidney-bladder model presented in ICRP publication 106
(addendum 3 to ICRP publication 53)$^{19}$, with the following formula:

$$N_b = f_s \sum \alpha_i \left[ \frac{1 - \exp(-\lambda_p t_b)}{\lambda_p} - \frac{1 - \exp(-(\lambda_i + \lambda_p) t_b)}{\lambda_i + \lambda_p} \right] \left[ \frac{1}{1 - \exp(-(\lambda_i + \lambda_p) t_b)} \right]$$

where $f_s$ is the fractional distribution to organ or tissue, $\alpha_i$ is the fraction of $f_s$ eliminated with the
 corresponding biological constant $\lambda_i$, $\lambda_p$ is the physical decay constant, and $t_b$ is the bladder filling
and voiding interval (considered a constant of 3.5 h in adults).

Kidney and bladder are the organs that received the highest dose after administration of
phosphonates such as HEDP, because they are mainly eliminated by the kidney. Thus, the number
of disintegrations in the kidney ($N_K$) was calculated using the kidney-bladder model from ICRP 53
with the following formula (considering both kidney uptake and the activity that passes through this organ due to excretion):

\[ N_K = f_K \left[ 1 - \exp(-\lambda_p t_K) \right] \sum_i \frac{\lambda_i}{\lambda_i + \lambda_p} \]

where \( f_K \) is the kidney fractional distribution and \( t_K \) is the mean transit time of phosphonates in the kidney. The other 3 radiopharmaceuticals are eliminated predominantly by the gastro-intestinal (GI) system; therefore, the number of disintegrations that occurred in this tract were calculated using the GI model of the OLINDA/EXM 1.1 software\(^{20}\), which is based on the ICRP 30 GI model\(^{21}\).

### 2.1 Dose Calculations

Each organ’s absorbed dose was calculated for each Tc radioisotope with the OLINDA/EXM 1.1 and OLINDA/EXM 2.0 software codes. The OLINDA version 1.1 makes use of anthropomorphic phantoms based on the Oak Ridge models, which employs geometrical shapes to define the organs and calculates the effective dose using the tissue weighting factors recommended by ICRP 60\(^{22}\). In version 2.0, the geometrical models were replaced by the realistic NURBS-type models, based on the recent standardized masses defined by the ICRP in its publication 89\(^{23}\), and the tissue weighting factors were implemented in accordance with the recommendations of ICRP 103\(^{24}\).

Both versions of OLINDA/EXM software use the RADAR dose system and calculate the equivalent dose in each organ according to the general equation:

\[ D_{\text{target--source}} = N_{\text{source}} \times DF_{\text{target--source}} \]

where \( N_{\text{source}} \) is the number of disintegrations that occur in the source organ per unit of activity administered (MBq-h/MBq) and \( DF \) is a dose factor that depends on the radionuclide used and on the spatial relationship between the target and the source organs, and on their tissue compositions.

The dose factor \( DF \) is given as:

\[ DF = \frac{k \sum n_i E_i \phi_i w_k}{m} \]
where \( m \) is the mass of the target organ, \( n_i \) is the number of \( i \)-th nuclear transitions per nuclear transformation, \( E_i \) is the mean energy of the \( i \)-th nuclear transition, \( \phi_i \) is the absorbed fraction in the target organ of radiation energy \( E_i \) emitted from the source organ, \( w_R \) is the radiation weighting factor assigned to the \( i \)-th radiation and \( k \) is a constant (which value depends on the units of the included quantities).

To calculate the equivalent dose in the main organs delivered from the radiopharmaceuticals labelled with each one of the Tc radioisotopes present in the CP-\(^{99m}\)Tc solution, the number of disintegrations of all source organs calculated for each radionuclide and the adult male phantom were used as program inputs with both versions of OLINDA/EXM software. Effective dose (ED) for each Tc radioisotope was calculated by OLINDA as the tissue-weighted sum of the equivalent doses. Total effective dose \((ED_t)\) produced by the CP-\(^{99m}\)Tc was calculated at 5 different times after irradiation (6, 8, 10, 12 and 15 h) using the following equation:

\[
ED_t = \sum_i f_i ED_i
\]

where \( f_i \) is the fraction of total activity corresponding to each radioisotope \( i \) and \( ED_i \) is the effective dose contribution per unit of activity from each radioisotope \( i \). The values for \( f_i \) parameters were obtained from the experimental results found in the framework of the TECHN_OSP/LARAMED research project on cyclotron-Tc production. The relative activities of \(^{99m}\)Tc and the other technetium isotopes, obtained after irradiation of \(^{100}\)Mo-enriched (99.05\%) metallic targets with 15.7 MeV proton beam for 60 min, were used as reference data. The target irradiation was carried out on the model PETtrace 16-9 medical cyclotron, located at St. Orsola-Malpighi Hospital, Nuclear Medicine Department (Bologna, Italy). Table 1 shows the average of relative activities of the technetium nuclides in the extracted solutions, obtained from 3 experiments and calculated at the EOB. Table 2 shows the radionuclide’s impurity limits for human use of sodium pertechnetate, reported by the European Pharmacopoeia, version 9.3, and the fraction of the total activity corresponding to each Tc-radioisotope calculated for the five time points after EOB studied.
Table 1. Technetium-nuclide relative activities in the extracted solution calculated for EOB (see text for irradiation parameters).

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Physical half-life (h)</th>
<th>Radioactive concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc</td>
<td>6.01</td>
<td>96.59 ± 0.62</td>
</tr>
<tr>
<td>$^{97m}$Tc</td>
<td>2193.6</td>
<td>0.001130 ± 0.000064</td>
</tr>
<tr>
<td>$^{96}$Tc</td>
<td>102.72</td>
<td>0.0273 ± 0.0033</td>
</tr>
<tr>
<td>$^{95}$Tc</td>
<td>20</td>
<td>0.1229 ± 0.0243</td>
</tr>
<tr>
<td>$^{95m}$Tc</td>
<td>1464</td>
<td>0.00063 ± 0.00013</td>
</tr>
<tr>
<td>$^{94}$Tc</td>
<td>4.88</td>
<td>0.1577 ± 0.0367</td>
</tr>
<tr>
<td>$^{94m}$Tc</td>
<td>0.87</td>
<td>0.8932 ± 0.3868</td>
</tr>
<tr>
<td>$^{93}$Tc</td>
<td>2.75</td>
<td>0.05429 ± 0.01214</td>
</tr>
<tr>
<td>$^{93m}$Tc</td>
<td>0.73</td>
<td>2.15 ± 0.09</td>
</tr>
</tbody>
</table>

Table 2. Radionuclide impurity limits reported by the European Pharmacopoeia, version 9.3, and the fraction of the total activity corresponding to each Tc-radioisotope in the extracted solution, calculated for five different time points after EOB.

<table>
<thead>
<tr>
<th>Pharmacopoeia Limit</th>
<th>Fraction of technetium isotopes contribution to the total activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$^{99m}$Tc</td>
</tr>
<tr>
<td>Time after EOB (h)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>96.59</td>
</tr>
<tr>
<td>6</td>
<td>99.54</td>
</tr>
<tr>
<td>8</td>
<td>99.53</td>
</tr>
<tr>
<td>10</td>
<td>99.49</td>
</tr>
<tr>
<td>12</td>
<td>99.43</td>
</tr>
<tr>
<td>15</td>
<td>99.31</td>
</tr>
</tbody>
</table>

3. RESULTS

The total number of disintegrations in the main source organs depends directly on the pharmacokinetics of each complex and on the half-life of the radionuclide. The calculated values, for each Tc-radioisotope after administration of Tc-pertechnetate, Tc-HEDP and Tc-HMPAO radiopharmaceuticals are summarized in Table 3. For each radiopharmaceutical, $^{97m}$Tc and $^{95m}$Tc
are the radionuclides that produced the highest number of the disintegrations per unit of administered activity (see table 3), due to their long half-life.

**Table 3.** Calculated number of disintegrations in the source organs per each MBq of $^{99m}$Tc-radiopharmaceuticals administered.

<table>
<thead>
<tr>
<th>Source organ</th>
<th>$^{99m}$Tc</th>
<th>$^{97m}$Tc</th>
<th>$^{95}$Tc</th>
<th>$^{93m}$Tc</th>
<th>$^{92}$Tc</th>
<th>$^{94m}$Tc</th>
<th>$^{95}$Tc</th>
<th>$^{93m}$Tc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tc-Pertechnetate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.037</td>
<td>0.068</td>
<td>0.064</td>
<td>0.052</td>
<td>0.067</td>
<td>0.035</td>
<td>0.015</td>
<td>0.027</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>0.056</td>
<td>0.101</td>
<td>0.096</td>
<td>0.078</td>
<td>0.101</td>
<td>0.052</td>
<td>0.022</td>
<td>0.041</td>
</tr>
<tr>
<td>Stomach content</td>
<td>0.179</td>
<td>0.200</td>
<td>0.199</td>
<td>0.193</td>
<td>0.200</td>
<td>0.175</td>
<td>0.111</td>
<td>0.160</td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.247</td>
<td>0.288</td>
<td>0.286</td>
<td>0.275</td>
<td>0.288</td>
<td>0.239</td>
<td>0.134</td>
<td>0.212</td>
</tr>
<tr>
<td>Small intestine content</td>
<td>0.548</td>
<td>0.799</td>
<td>0.779</td>
<td>0.703</td>
<td>0.799</td>
<td>0.510</td>
<td>0.191</td>
<td>0.398</td>
</tr>
<tr>
<td>Upper large int. walls</td>
<td>0.379</td>
<td>1.506</td>
<td>1.341</td>
<td>0.878</td>
<td>1.501</td>
<td>0.308</td>
<td>0.027</td>
<td>0.156</td>
</tr>
<tr>
<td>Upper large int. content</td>
<td>0.712</td>
<td>2.586</td>
<td>2.328</td>
<td>1.587</td>
<td>2.579</td>
<td>0.583</td>
<td>0.054</td>
<td>0.303</td>
</tr>
<tr>
<td>Lower large int. content</td>
<td>0.349</td>
<td>4.737</td>
<td>3.698</td>
<td>1.574</td>
<td>4.708</td>
<td>0.244</td>
<td>0.005</td>
<td>0.079</td>
</tr>
<tr>
<td>Bladder content</td>
<td>0.342</td>
<td>0.963</td>
<td>0.807</td>
<td>0.554</td>
<td>0.958</td>
<td>0.306</td>
<td>0.063</td>
<td>0.209</td>
</tr>
<tr>
<td>Others</td>
<td>4.318</td>
<td>28.533</td>
<td>20.711</td>
<td>9.908</td>
<td>28.267</td>
<td>3.678</td>
<td>0.852</td>
<td>2.324</td>
</tr>
</tbody>
</table>

| Tc-HEDP              |            |            |           |            |           |            |           |
| Bone                 | 2.953      | 35.453     | 21.619    | 8.119      | 34.904    | 2.443      | 0.425     | 1.423     | 0.346     |
| Kidneys              | 0.125      | 0.869      | 0.553     | 0.245      | 0.856     | 0.113      | 0.062     | 0.088     | 0.060     |
| Bladder content      | 1.147      | 2.151      | 1.856     | 1.490      | 2.139     | 1.072      | 0.319     | 0.833     | 0.256     |
| Total body           | 4.005      | 41.310     | 25.492    | 10.031     | 40.683    | 3.448      | 0.896     | 2.213     | 0.777     |

| Tc-HMPAO             |            |            |           |            |           |            |
| Brain                | 0.407      | 6.635      | 3.580     | 1.194      | 6.499     | 0.335      | 0.062     | 0.193     | 0.052     |
| Thyroid              | 0.044      | 0.356      | 0.249     | 0.110      | 0.353     | 0.037      | 0.008     | 0.022     | 0.007     |
| Lung                 | 0.708      | 8.585      | 5.226     | 1.953      | 8.451     | 0.587      | 0.118     | 0.347     | 0.100     |
| Liver                | 0.505      | 1.372      | 1.243     | 0.890      | 1.369     | 0.446      | 0.131     | 0.306     | 0.114     |
| Gall bladder content | 0.097      | 0.130      | 0.127     | 0.118      | 0.130     | 0.092      | 0.039     | 0.075     | 0.035     |
| Stomach wall         | 0.047      | 0.736      | 0.398     | 0.134      | 0.721     | 0.039      | 0.008     | 0.023     | 0.007     |
| Small intestine wall | 0.203      | 3.170      | 1.716     | 0.579      | 3.106     | 0.168      | 0.033     | 0.099     | 0.028     |
| Upper large int. wall| 0.066      | 1.030      | 0.558     | 0.188      | 1.099     | 0.055      | 0.011     | 0.032     | 0.009     |
| Lower large int. wall| 0.050      | 0.781      | 0.423     | 0.143      | 0.765     | 0.041      | 0.008     | 0.024     | 0.007     |
| Stomach content      | 0.006      | 0.007      | 0.007     | 0.006      | 0.007     | 0.074      | 0.004     | 0.005     | 0.003     |
| Small intestine content | 0.233  | 0.340      | 0.331     | 0.299      | 0.339     | 0.189      | 0.081     | 0.169     | 0.071     |
| Upper large int. content | 0.303  | 1.099      | 0.989     | 0.669      | 1.096     | 0.216      | 0.023     | 0.129     | 0.017     |
| Lower large int. content | 0.148  | 2.013      | 1.572     | 0.675      | 2.001     | 0.091      | 0.002     | 0.034     | 0.001     |
| Kidneys              | 0.624      | 3.082      | 2.526     | 1.416      | 3.066     | 0.527      | 0.109     | 0.320     | 0.007     |
| Bladder content      | 0.546      | 1.472      | 1.199     | 0.818      | 1.463     | 0.500      | 0.134     | 0.373     | 0.107     |
| Others               | 2.993      | 24.504     | 17.147    | 7.546      | 24.248    | 2.515      | 0.570     | 1.545     | 0.488     |
It has been demonstrated that the concentration of Tc-MIBI in the source organs can change depending on whether the myocardial perfusion test is carried out in stress or rest conditions\textsuperscript{25}; thus, the total number of disintegrations in the main source organs after MIBI administration was calculated considering both stress and rest models. Table 4 shows in general, a higher number of disintegrations in the source organs when the test was performed in rest conditions because the Tc-MIBI-concentration in the source organs increases. Muscle and heart are the only organs that present a higher number of disintegrations during the myocardial perfusion test in stress conditions.

Table 4. Calculated number of disintegrations in the source organs per each MBq of Tc-MIBI administered, using both stress and rest models.

<table>
<thead>
<tr>
<th>Source organ</th>
<th>Number of disintegrations per unit of administered activity (MBq h/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>99mTc</td>
</tr>
<tr>
<td><strong>Tc-MIBI (rest)</strong></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>0.069</td>
</tr>
<tr>
<td>Liver</td>
<td>0.674</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>0.246</td>
</tr>
<tr>
<td>Small intestine content</td>
<td>0.496</td>
</tr>
<tr>
<td>Upper large int. content</td>
<td>0.644</td>
</tr>
<tr>
<td>Lower large int. content</td>
<td>0.316</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.653</td>
</tr>
<tr>
<td>Bladder content</td>
<td>0.190</td>
</tr>
<tr>
<td>Muscles</td>
<td>1.387</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>0.104</td>
</tr>
<tr>
<td>Thyroids</td>
<td>0.006</td>
</tr>
<tr>
<td>Others</td>
<td>3.120</td>
</tr>
<tr>
<td><strong>Tc-MIBI (stress)</strong></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>0.092</td>
</tr>
<tr>
<td>Liver</td>
<td>0.530</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>0.202</td>
</tr>
<tr>
<td>Small int. content</td>
<td>0.385</td>
</tr>
<tr>
<td>Upper large int. cont.</td>
<td>0.501</td>
</tr>
<tr>
<td>Lower large int. cont.</td>
<td>0.246</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.466</td>
</tr>
<tr>
<td>Bladder content</td>
<td>0.151</td>
</tr>
<tr>
<td>Muscles</td>
<td>2.774</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>0.069</td>
</tr>
<tr>
<td>Thyroids</td>
<td>0.004</td>
</tr>
<tr>
<td>Others</td>
<td>2.566</td>
</tr>
</tbody>
</table>
Radiopharmaceutical effective doses (ED) calculated for each Tc radioisotope are summarized in table 5. The small difference in the effective dose values, obtained with both versions of OLINDA/EXM software, is attributable to the divergence in the tissue weighting factors and the phantom models used by each version.

**Table 5.** Radiopharmaceuticals effective doses calculated using both versions of OLINDA/EXM for each Tc radioisotope

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Tc-Pertechnetate</th>
<th>Tc-HEDP</th>
<th>Tc-HMPAO</th>
<th>Tc-MIBI rest</th>
<th>Tc-MIBI stress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OLINDA/EXM 1.1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99mTc</td>
<td>1.07E-02</td>
<td>6.42E-03</td>
<td>9.25E-03</td>
<td>7.94E-03</td>
<td>6.84E-03</td>
</tr>
<tr>
<td>97mTc</td>
<td>1.44E-01</td>
<td>4.45E-02</td>
<td>1.99E-01</td>
<td>1.14E-01</td>
<td>9.01E-02</td>
</tr>
<tr>
<td>96mTc</td>
<td>4.71E-01</td>
<td>3.71E-01</td>
<td>5.06E-01</td>
<td>4.21E-01</td>
<td>3.83E-01</td>
</tr>
<tr>
<td>95mTc</td>
<td>8.87E-02</td>
<td>5.55E-02</td>
<td>8.01E-02</td>
<td>7.67E-02</td>
<td>6.94E-02</td>
</tr>
<tr>
<td>95mTc</td>
<td>1.90E-01</td>
<td>1.66E-01</td>
<td>2.40E-01</td>
<td>1.63E-01</td>
<td>1.46E-01</td>
</tr>
<tr>
<td>94mTc</td>
<td>1.13E-01</td>
<td>7.99E-02</td>
<td>9.55E-02</td>
<td>9.14E-02</td>
<td>8.19E-02</td>
</tr>
<tr>
<td>94mTc</td>
<td>6.58E-02</td>
<td>3.63E-02</td>
<td>4.54E-02</td>
<td>3.70E-02</td>
<td>2.26E-02</td>
</tr>
<tr>
<td>93mTc</td>
<td>4.23E-02</td>
<td>3.18E-02</td>
<td>3.33E-02</td>
<td>3.14E-02</td>
<td>2.78E-02</td>
</tr>
<tr>
<td>93mTc</td>
<td>1.12E-02</td>
<td>6.73E-03</td>
<td>6.86E-03</td>
<td>5.71E-03</td>
<td>4.79E-03</td>
</tr>
<tr>
<td><strong>OLINDA/EXM 2.0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99mTc</td>
<td>1.07E-02</td>
<td>5.24E-03</td>
<td>8.64E-03</td>
<td>8.09E-03</td>
<td>7.04E-03</td>
</tr>
<tr>
<td>97mTc</td>
<td>1.50E-01</td>
<td>3.82E-02</td>
<td>1.88E-01</td>
<td>1.22E-01</td>
<td>1.00E-01</td>
</tr>
<tr>
<td>96mTc</td>
<td>3.67E-01</td>
<td>3.06E-01</td>
<td>4.37E-01</td>
<td>3.44E-01</td>
<td>3.16E-01</td>
</tr>
<tr>
<td>95mTc</td>
<td>7.29E-02</td>
<td>4.52E-02</td>
<td>6.97E-02</td>
<td>6.74E-02</td>
<td>6.09E-02</td>
</tr>
<tr>
<td>95mTc</td>
<td>1.55E-01</td>
<td>1.39E-01</td>
<td>2.13E-01</td>
<td>1.38E-01</td>
<td>1.25E-01</td>
</tr>
<tr>
<td>94mTc</td>
<td>1.02E-01</td>
<td>6.31E-02</td>
<td>8.68E-02</td>
<td>8.32E-02</td>
<td>7.46E-02</td>
</tr>
<tr>
<td>94mTc</td>
<td>6.92E-02</td>
<td>2.94E-02</td>
<td>3.97E-02</td>
<td>3.54E-02</td>
<td>2.44E-02</td>
</tr>
<tr>
<td>93mTc</td>
<td>3.95E-02</td>
<td>2.48E-02</td>
<td>3.05E-02</td>
<td>2.87E-02</td>
<td>2.55E-02</td>
</tr>
<tr>
<td>93mTc</td>
<td>1.30E-02</td>
<td>6.09E-03</td>
<td>7.05E-03</td>
<td>6.08E-03</td>
<td>5.26E-03</td>
</tr>
</tbody>
</table>

Table 6 shows the total effective dose (mSv/MBq) calculated with both software versions, for the radiopharmaceuticals prepared with pure 99mTc eluted from a generator (GP-99mTc) and the 99mTc produced by the cyclotron at different time points after EOB. The increase in effective dose to the patient (in percent), caused by the presence of the other Tc-radionuclides, is also reported in this table.

In general the values of effective dose calculated with version 2.0 of OLINDA/EXM decreased for Tc-HEDP and Tc-HMPAO, remained the same for Tc-pertechnetate, and increased for Tc-MIBI, compared to those obtained using version 1.1 (Table 6). The difference in effective dose after
administration of CP-\(^{99m}\)Tc and GP-\(^{99m}\)Tc labelled-radiopharmaceuticals were lower using OLINDA/EXM 2.0 except for the case of Tc-HEDP, in which the values remained invariable. All radiopharmaceuticals showed greater differences in effective doses after 15 h of EOB, because the concentration of impurities increases over the time, as shown in table 2.

**Table 6.** Total effective dose (\(ED_t\)) calculated for GP-\(^{99m}\)Tc and CP-\(^{99m}\)Tc radiopharmaceuticals and percent of patient dose increase (\(DI\)) after administration of CP-\(^{99m}\)Tc radiopharmaceuticals at different time points after EOB.

<table>
<thead>
<tr>
<th>OLINDA/EXM 1.1</th>
<th>Calculated total effective dose (mSv/MBq) and dose increase for each radiopharmaceutical</th>
<th>Tc-Pertechnetate</th>
<th>Tc-HEDP</th>
<th>Tc-HMPAO</th>
<th>Tc-MIBI rest</th>
<th>Tc-MIBI stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labelled with GP-(^{99m})Tc</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
</tr>
<tr>
<td>Time after EOB</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
</tr>
<tr>
<td>6 h</td>
<td>1.13E-02</td>
<td>5.34</td>
<td>6.83E-03</td>
<td>6.44</td>
<td>9.80E-03</td>
<td>5.96</td>
</tr>
<tr>
<td>8 h</td>
<td>1.13E-02</td>
<td>6.04</td>
<td>6.89E-03</td>
<td>7.31</td>
<td>9.88E-03</td>
<td>6.84</td>
</tr>
<tr>
<td>10 h</td>
<td>1.14E-02</td>
<td>6.97</td>
<td>6.96E-03</td>
<td>8.47</td>
<td>9.99E-03</td>
<td>7.99</td>
</tr>
<tr>
<td>12 h</td>
<td>1.16E-02</td>
<td>8.15</td>
<td>7.06E-03</td>
<td>9.92</td>
<td>1.01E-02</td>
<td>9.41</td>
</tr>
<tr>
<td>15 h</td>
<td>1.18E-02</td>
<td>10.47</td>
<td>7.24E-03</td>
<td>12.80</td>
<td>1.04E-02</td>
<td>12.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OLINDA/EXM 2.0</th>
<th>Calculated total effective dose (mSv/MBq) and dose increase for each radiopharmaceutical</th>
<th>Tc-Pertechnetate</th>
<th>Tc-HEDP</th>
<th>Tc-HMPAO</th>
<th>Tc-MIBI rest</th>
<th>Tc-MIBI stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labelled with GP-(^{99m})Tc</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
<td>(ED_t)</td>
</tr>
<tr>
<td>Time after EOB</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
<td>(DI) (%)</td>
</tr>
<tr>
<td>6 h</td>
<td>1.11E-02</td>
<td>4.40</td>
<td>5.57E-03</td>
<td>6.41</td>
<td>9.12E-03</td>
<td>5.57</td>
</tr>
<tr>
<td>8 h</td>
<td>1.12E-02</td>
<td>4.92</td>
<td>5.62E-03</td>
<td>7.30</td>
<td>9.19E-03</td>
<td>6.38</td>
</tr>
<tr>
<td>10 h</td>
<td>1.13E-02</td>
<td>5.64</td>
<td>5.68E-03</td>
<td>8.47</td>
<td>9.28E-03</td>
<td>7.43</td>
</tr>
<tr>
<td>12 h</td>
<td>1.14E-02</td>
<td>6.56</td>
<td>5.76E-03</td>
<td>9.94</td>
<td>9.40E-03</td>
<td>8.74</td>
</tr>
<tr>
<td>15 h</td>
<td>1.16E-02</td>
<td>8.37</td>
<td>5.91E-03</td>
<td>12.85</td>
<td>9.62E-03</td>
<td>11.33</td>
</tr>
</tbody>
</table>

Figure 1 shows the contribution (in percentage) of each Tc-radionuclide to the radiopharmaceutical’s effective dose at 3 different time points after EOB (8, 10 and 12h), calculated with both versions of OLINDA/EXM. Data for MIBI are reported only for stress condition because, in this case, the DI is higher than in rest conditions. As expected, \(^{99}\)Tc is the radioisotope
with greatest contribution to the effective dose, followed by $^{95}$Tc and $^{94}$Tc; the contribution of other Tc-radioisotopes is quite low, being at least 3 orders of magnitude smaller than the contribution of $^{99m}$Tc.
Figure 1. Contribution (in percentage) of each Tc-radionuclide to the effective dose of radiopharmaceuticals at 3 different time points after EOB (8, 10 and 12h) calculated with both versions of OLINDA/EXM.
4. DISCUSSION

The number of disintegrations in the main source organs calculated for each Tc-radioisotope after administration of Tc-pertechnetate, Tc-HEDP and Tc-MIBI are in general agreement with the data reported by Hou et al\textsuperscript{10}. However, some differences were found. The authors did not consider 3 important source organs (salivary gland, stomach content and upper large intestine walls) reported in the ICRP biokinetic model to calculate the dose produced by Tc-pertechnetate. They also underestimated the number of disintegrations for the Tc-MIBI model since liver delay and gallbladder uptake were not considered for the calculation. The greatest difference was found in the number of disintegrations of the total body calculated with the Tc-HEDP biokinetic model, because their calculated values range from half to 9 times less the values reported in table 3. It is not possible to determine whether these differences produced a considerable effect on the calculated total effective dose, by comparison with the results of the present work, because Hou et al did not report the total effective dose values, but rather, the percent of difference between cyclotron and reactor-produced technetium\textsuperscript{10}.

In general, low differences between the total effective doses calculated with both versions of the OLINDA software were expected, because version 2.0 uses more anatomically-accurate NURBS phantoms. Furthermore, some tissue-weighting factor values differ from the version 1.1 (ICRP 60) to version 2.0 (ICRP 103), resulting in an increment in the tissue equivalent dose, as in the case of Tc-MIBI, where the rise of muscle-weighting factor from 0.005 to 0.01 produced higher total effective doses using OLINDA/EXM 2.0 (see Table 6). However, the DI remained within the 10 % limit from 6 to 12 h after EOB for all of the radiopharmaceuticals labelled with the CP\textsuperscript{99m}Tc studied, when the more accurate version of Olinda/EXM 2.0 was used.

Table 6 shows that the percent of increase in dose is different for each radiopharmaceutical because the biological half-life in each source organ differs among compounds. Therefore, dose calculation must be done for each radiopharmaceutical in order to determine the range of time after the EOB in which the Tc-radiopharmaceutical can be administered to remain within the 10 % limit of DI.
The greatest time dependence in the DI contribution from Tc-radionuclides in the studied time intervals was found for $^{94m}$Tc and $^{93m}$Tc, since their impact on the dose decreases quickly. Although these Tc-radionuclides present the highest concentration in the CP-$^{99m}$Tc solution at the EOB, their contribution to the dose 6 h later will be minimal due to their short half-life (see Table 2). Radionuclides such as $^{97m}$Tc, $^{96}$Tc, and $^{95m}$Tc, having a longer half-life, should instead increase their dose contribution over time; however, due to the small concentrations in the reaction mixture, the increment is negligible (see fig 1).

Table 7 compares the increase of the total effective doses for three Tc-radiopharmaceuticals calculated from our experimental results, with the theoretical calculations from Hou et al $^{10}$ using the same Isoflex Mo target enriched to 99.05%, irradiated for 3h with a proton beam of 16 MeV. Dose contribution of Tc-impurities calculated by Hou also using OLINDA/EXM 1.1 software, is higher due to the longer irradiation time. Twelve hours after EOB, the increase in effective dose is greater than 10% for Tc-pertechnetate and Tc-MIBI, only Tc-HEDP DI remained under 10%. However, this is probably a consequence of the underestimation of the number of Tc-HEDP disintegrations in the whole body. Selivanova et al reported a 7.58 % increase in Tc-pertechnetate effective dose, assuming an irradiation at 24 MeV for two hours and injection time 6 hours after EOB, which is superior to the 5.30% obtained in this work for the same Mo target and injection time. This increment is the consequence of a greater production of $^{94}$Tc, $^{95}$Tc and $^{96}$Tc-radionuclides at 24 MeV.

$^{96}$Tc was the radioisotope with the highest contribution to the effective dose and is potentially detrimental to the image quality, due to its energetic $\gamma$ rays. Thus, the best CP-$^{99m}$Tc method should be one that produces the least amount of $^{96}$Tc. Using a proton beam of 15.7 MeV and an enriched Isoflex Mo target (99.05 %) it was found that just 0.0267% of the total activity is related to $^{96}$Tc (see Table 1). Selivanova et al$^{26}$ reported a $^{96}$Tc concentration in the Tc-final product of 0.0695%, 0.1478% and 0.1614% using the same type of Mo target and proton beams of 20, 22 and 24 MeV, respectively. These results demonstrate that the low-energy conventional medical
cyclotron is preferable, since it produces $^{99m}$Tc with less concentration of $^{96}$Tc than medium-energy cyclotrons, as preliminary reported in the theoretical study by Esposito et al.

**Table 7.** Comparison of the increase of total effective dose calculated in this study (15.7 MeV and 1h irradiation) for three Tc-radiopharmaceuticals with the values reported in the literature by Hou et al (16 MeV and 3 h irradiation).

<table>
<thead>
<tr>
<th>Irradiation data</th>
<th>Radiopharmaceuticals</th>
<th>15.7 MeV (1 h)</th>
<th>16 MeV (3 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time after EOB</td>
<td>Time after EOB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 h</td>
<td>12 h</td>
</tr>
<tr>
<td>$^{99m}$Tc-pertechnetate</td>
<td>5.99 %</td>
<td>8.07 %</td>
<td>8.28 %</td>
</tr>
<tr>
<td>$^{99m}$Tc-HEDP</td>
<td>7.25 %</td>
<td>9.82 %</td>
<td>7.49 %</td>
</tr>
<tr>
<td>$^{99m}$Tc-MIBI rest</td>
<td>7.05 %</td>
<td>9.57 %</td>
<td>9.23 %</td>
</tr>
</tbody>
</table>

To calculate the maximum patient radiation dose increase after the administration of the CP-$^{99m}$Tc-radiopharmaceuticals, the total effective dose values were multiplied by the maximum activity used in clinical practice for each type of diagnostic radiopharmaceutical. Table 8 shows the maximum radiation dose that a patient could receive after the administration of radiopharmaceuticals labelled with GP-$^{99m}$Tc and CP-$^{99m}$Tc, assuming the Tc impurity levels in the limits established by the European Pharmacopoeia (see table 2) and the Tc impurities obtained in our experimental studies. Analysing these values, it is clear that the increment of the dose due to the impurities is minimal. In all cases, patient radiation dose is lower than the maximum dose accepted for an imaging study (10 mSv) and also, than the dose received by patients after the administration of 370 MBq of $^{18}$FDG (7.03 mSv).

**Table 8.** Maximum patient radiation dose after the administration of radiopharmaceuticals labelled with technetium from different sources.
CONCLUSIONS

The percent of increase in dose is different for each radiopharmaceutical because the biological half-life in each source organ differs among compounds. Therefore, to determine the range of time after EOB in which the Tc-solution can be used, it is necessary to perform dosimetric studies with the most representative radiopharmaceuticals, not just with Tc-pertechnetate.

Comparing the results obtained using the data of our target irradiation experiments with the data reported by other research groups, it was concluded that the CP-\(^{99m}\)Tc, produced at lower energy (16 MeV) for shorter irradiation time (60 min), shows some advantages. Because, although the quantity of \(^{99m}\)Tc produced in this way is lower, its radionuclidic purity is higher, and the solution can be used for a longer period of time without increasing the patient absorbed dose substantially.

The patient radiation absorbed dose increase by the contribution of Tc contaminant activity present in the cyclotron-\(^{99m}\)Tc solution, produced by the beam irradiation conditions reported in this work, is relatively low. However, its impact should not be underestimated. Based on this data, it was concluded that although the concentrations of two radionuclides \(^{94}\)Tc and \(^{95}\)Tc in the CP-\(^{99m}\)Tc, is outside the limits established by the European Pharmacopoeia for all the time points studied, radiopharmaceuticals labelled with this CP-\(^{99m}\)Tc solution administered from 6 to 12 h after the end

<table>
<thead>
<tr>
<th>(^{99m})Tc Source</th>
<th>(Tc\text{-pertechnetate (250 MBq)})</th>
<th>(Tc\text{-HEDP (1000 MBq)})</th>
<th>(Tc\text{-HMPAO (185 MBq)})</th>
<th>(Tc\text{-MIBI rest (740 MBq)})</th>
<th>(Tc\text{-MIBI stress (740 MBq)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(GP\text{-}(^{99m})Tc)</td>
<td>(1.1)</td>
<td>(2.0)</td>
<td>(1.1)</td>
<td>(2.0)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>(CP\text{-}(^{99m})Tc) with the pharmacopoeial limits</td>
<td>(2.68)</td>
<td>(6.42)</td>
<td>(5.24)</td>
<td>(1.71)</td>
<td>(1.60)</td>
</tr>
<tr>
<td>(CP\text{-}(^{99m})Tc)</td>
<td>(2.79)</td>
<td>(6.77)</td>
<td>(5.52)</td>
<td>(1.80)</td>
<td>(1.68)</td>
</tr>
</tbody>
</table>

\(\text{Time after EOB (h)}\)

| \(6\) | \(2.82\) | \(6.83\) | \(5.57\) | \(1.81\) | \(1.69\) | \(6.24\) | \(6.30\) | \(5.39\) | \(5.49\) |
| \(8\) | \(2.84\) | \(6.89\) | \(5.62\) | \(1.83\) | \(1.70\) | \(6.29\) | \(6.34\) | \(5.44\) | \(5.53\) |
| \(10\) | \(2.86\) | \(6.96\) | \(5.68\) | \(1.85\) | \(1.72\) | \(6.36\) | \(6.39\) | \(5.50\) | \(5.58\) |
| \(12\) | \(2.89\) | \(7.06\) | \(5.76\) | \(1.87\) | \(1.74\) | \(6.44\) | \(6.46\) | \(5.58\) | \(5.64\) |
of bombardment could be used in routine nuclear medicine diagnostic studies because, the dose increment remained within the 10% limit.

5. ACKNOWLEDGMENTS

Authors would like to thank the Italian National Institute of Nuclear Physics (INFN) for the full financial support received for this work. It has been carried out within the TECHN-OSP research program (2015-2017) approved by the CSN5 Committee. This study was also part the Coordinated Research Project (CRP-F22062) promoted by the International Atomic Energy Agency (IAEA) (2011–2015), which support is gratefully acknowledged.

The authors have no conflicts of interest to disclose.

6. REFERENCES


18. ICRP. Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). *ICRP Publication 80*. 1998;Ann. ICRP 28;(3).


