


A brief review of targeted radionuclide therapies

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Abstract

Personalized medicine is an emerging medical field. Targeted radionuclide therapies for benign and malignant diseases have been in use since 1945. Over the last 20 years due to advancements in the nanotechnology and targeting cell receptors, radionuclide therapies have emerged as a subspecialty of nuclear medicine. Through this article we would like to briefly describe the evolution of radionuclide therapies and their different clinical applications as personalized medicine.

Key words: Radionuclide therapy, 131I-metaiodobenylguanidine therapy, CD-20 targeted therapies, radioembolization, metastatic bone pain palliation

Introduction

Radiotherapy techniques have proved important in treating as well as prolonging the patients' lives depending on the type of cancer in question. However, the success of these techniques is limited by their lack of specificity as the anti-cancer agents or cytotoxic technologies do no distinguish between the cancerous regions and the normal tissues [1]. Most of the traditionally used radiotherapy techniques apply a non-discriminatory destruction of the cells exhibiting uncontrolled growth without any degree of selection leading to the destruction of the healthy cells. Unlike external radiotherapy which damages cells' DNA with the aim of killing those with uncontrolled growth, targeted radionuclide therapy offers a systemic treatment by delivering toxic levels of radiolabelled molecules to the target sites for a highly selective destruction of the site [2]. Radionuclide therapy acts the same way as chemotherapy by targeting specific cells, but it is more advanced in that radionuclides also kill tumour cells lacking tumour-specific receptors and thus it has ability for direct as well as a bystander effect which ultimately kills the tumour cells. The biological effect of targeted radionuclide therapy results from energy absorption of radiation emitted by the radionuclide. After the first description of radioimmunotherapy by Korngold and Pressman in 1953, numerous radio-pharmaceuticals have been developed by advanced techniques in genetic engineering.
and chelating techniques [3]. Targetted radiotherapy involves the utilization of three particulate particles, which are capable of irradiating tissue volumes with subcellular, cellular and multicellular dimensions. These particles include Auger electrons, alpha particles, and beta particles.

**Auger electrons and Auger-electron-emitting radionuclides**

Auger electrons are particles released by some elements in a phenomenon referred to as the Auger effect. In this phenomenon, an atom emits an electron after filling an inner-shell vacancy resulting in energy release. Some of the current available or prospective Auger electron emitters include indium-111, iodine-125, iodine-123, and bromine-77. These radionuclides can be used alongside targeting vehicles to localize sub-cellular radiations near the cellular DNA leading to an effective and a specific killing of the tumour cells. Using auger-emitting radionuclide therapeutics, highly tailored targetted radiotherapeutics could be engineered to fit the specific needs of a cancer patient [4].

**Beta particles and beta-emitting radionuclides**

Beta particles are fast-moving electrons emitted by the nucleus during radioactive decay. Some of the currently approved beta-emitting radionuclides used in radiotherapy include yttrium-90 and iodine-131 (for non-Hodgkin's lymphoma treatment), strontium-89-chloride and samarium-153-EDTMP (for bone metastases). Other potential beta-emitting radionuclides include rhenium-186, gold-199, copper-67, rhenium-186, and lutetium-177 amongst others. The major advantage of beta particles is that they have minimal tissue penetration. These particles are emitted at high speed, but they become rapidly attenuated by biological tissues. As a result, when administered as a radiopharmaceutical it does not affect the surrounding tissues as it cannot travel beyond specific range within a biological structure. An additional protection of the un-targetted tissue is also achieved by radioimmuno targetted therapy [4].

**Alpha particles and alpha-emitting radionuclides**

Alpha particles comprise of two protons as well as two neutrons, and they are identical to helium atom's nucleus. Alpha-emitting radionuclides emit particles of only a few cell diameters in tissue. One of the advantages of alpha particles is that they have a high linear energy transfer that makes them more biologically effective as compared to the conventional radiotherapy techniques. In this vein, fewer alpha particles are capable of killing human cancer cells. Some of the available radionuclides that emit alpha particles include radium-223, astatine-211, and bismuth-2013. Alpha particles are preferred for radiotherapy for their ability to deliver lethal radiation, within a range of 50-90 µm in diameter. This allows the emitter to specifically target cancerous tissue without destroying the adjacent healthy tissues. Alpha particles offer a therapeutic benefit by breaking the DNA double strand and thus breaking the cell cycle. Also, these particles cause chromosomal instability in the nearby cells leading to a bystander effect as observed in radiotherapy [4].

**Radionuclides as therapeutics**

Radionuclides used in cancer treatment release energy in the form of beta particles, Auger electrons or alpha particles to cause the destruction of cancer cells and result in improvement of the patient's condition. The radionuclides applied for the purposes of treating cancer depend on several factors, including: the nuclear emission properties, mode of radioactive decay, physical half-life, radionuclide production route, pharmacological features of the resultant radio-conjugate, radiation type and its energy, and the stability of the resultant daughter nuclides. Most of the cancer-destroying radionuclides have a physical half-life of between 10 hours to 10 days allowing them to deposit a large radiation
dose. They also emit high LET radiation near the target cancer tissue and their daughter nuclides are stable and long-lived to increase the therapeutic effect of the radionuclide [5].

**Clinical Applications**

**Iodine-131 and thyroid cancer treatment**

Iodine-131 is highly radioactive and has a half-life of 8.02 days, and when used in small doses it is used in cancer treatment. When iodine-131 is taken orally, it crosses the gastrointestinal wall, and is concentrated in the thyroid gland where it decays into xenon-131, with the release of gamma radiations and beta particles.

On the global scale, the use of radioactive iodine in differentiated thyroid cancer treatment has been the most common and the oldest targeted radiotherapy. The aim of the use of iodine-131 in differentiated thyroid cancer treatment is to destroy cancer cells in order to ablate the remnant thyroid tissue in order to optimise follow-up and reduce cancer recurrence rate [6]. The significance of radioactive iodine treatment in targeted radiotherapy is derived from the ability of both the follicular and the papillary cancers to express sodium iodide symporter for radioactive iodine uptake by cancer cells. Low doses of radioactive iodine have high levels of efficacies as well as high safety profiles making it the most acceptable thyroid cancer management modality across the world. Furthermore, the disintegration of the respective radionuclides results in additional cytotoxic effects on the target cells [7].

**Neuroblastoma/neuroendocrine tumours and 131I-metaiodobenylguanidine**

Since the 1980s, treatment of neuroendocrine tumours have been treated using 131I-metaiodobenylguanidine (131I-MIBG) because of its high efficacy in treating chromaffin cell tumours (paraganglioma, pheochromocytoma, and neuroblastoma).

131I-MIBG uptake happens in a similar version to noradrenaline and increases after catecholamine excretion or adrenergic innervation. Stage III and IV patients with neuroblastoma are difficult to manage via chemotherapy and surgery and most cases resort to the administration of 131I-MIBG to control tumour growth as well as for symptom relief [8]. A management plan for neuroblastoma using 131I-MIBG involves taking the patient through a series of studies including tissue biopsies, MRI/CT studies, ultrasonography, 123I-MIBG scintigraphy and FDG-PET/CT before the commencement of 131I-MIBG therapy. Moreover, recommendations point that 131I-MIBG infusion should last for longer than one hour in order to avoid metaiodobenylguanidine side effects. 131I-MIBG may also be used for the treatment of other similar tumours such as paraganglioma, pheochromocytoma, medullary thyroid cancer, and carcinoid tumours. These tumours have a response rate of 30-75%, indicating high efficacies [9].

**Targetted radionuclide therapy and lymphoma treatment**

In the 2000s, two major targeted radionuclide therapeutic agents were introduced for lymphoma treatment to reduce the number of deaths resulting from low-grade lymphoma that is difficult to treat with chemotherapy techniques. These agents include I-131 tositumomab and Y-90 ibritumomabtiuxetan and they have been demonstrated to yield 50-80 percent response rates. I-131 tositumomab has an IgG2a murine anti-CD20 antibody (tositumomab), while Y-90 ibritumomabtiuxetan has murine IgG1 anti-CD20 antibody (ibritumomab), the difference between the two agents is their differential linkage to the radionuclide [10]. By targeting CD20 antigens, these agents deliver the respective radionuclides mature B-lymphocytes, pre-B lymphocytes, and B-cell non-Hodgkin’s lymphoma, and thus it ends up inducing apoptosis, antibody-dependent cytotoxicity, and complement-dependent cytotoxicity after the formation of the antibody-antigen immune complex [11].
**Yttrium-90 and liver tumours treatment**

Such metastatic tumours as pancreatic carcinoma, colorectal carcinoma, neuroendocrine tumours and breast cancers also occur in the liver after metastases leading to a fatal pathological burden. However, reduction of the burden is achieved through traditional therapies with an additional administration of Y-90 microspheres for radioembolization. Radioembolization of the liver cancers with Y-90 microspheres generate between 27 and 100 percent response rates in clinical treatments [12].

**Palliation of metastatic bone pain**

During advanced stages of cancers, bone pain reduces the quality of life of the cancer patient to a significant extent. However, the administration of radiopharmaceuticals can palliate pain from metastatic processes. Some of the approved metastatic pain palliation radiopharmaceuticals include $^{186}$Re-etidronate, $^{153}$Sm-lexidronam and $^{89}$Sr-chloride; their administrations result in high concentrations in bones leading to effective pain management [13].

**Application of radionuclide targeted therapy in haematological malignancies**

The type of radionuclide targeted therapy applied on a specific type of cancer is dependent on the type of malignancy in question. As a result, haematological malignancies require a different type of targeted radionuclide therapy from the one used for the solid tumours. In haematological malignancies, targeted radionuclide therapy is supported by three major factors. One of the reasons for the effectiveness of targeted radionuclide therapy is the expression of specific surface antigens by most cancer cell lines [14]. These antigens are absent from other tissues in the organism and thus making targeted therapies possible. Another reason for the effectiveness of this approach is the rich availability of the high-quality antibodies against antigens expressed by haematological tissues. Moreover, the effectiveness of this approach is also made possible by the high sensitivity of lymphomas and leukemias to ionizing radiation. In addition, the effectiveness of the targeted radionuclide therapy is also increased by the availability of bone marrow transplantation technologies that allow for the replenishment of the haematological stem cells after the treatment of haematological malignancies with high dose radionuclides. Some of the target antigens in targeted radionuclide treatment of haematological malignancies include CD45, CD66, CD33, CD5, CD25, and the most commonly targeted CD20. $^{90}$Y and $^{131}$I have the greatest potential for application as radionuclides in targeted radionuclide therapy. Moreover, some of the common haematological tumours treated using targeted radionuclide therapy includes T-cell leukemias, chronic lymphocytic leukemia, and Hodgkin's lymphoma [15].

**Application of radionuclide targeted therapy in solid malignancies**

Unlike the treatment of haematological tumours with targetted radionuclides which is highly efficacious, the treatment of solid tumours has low efficacies and is thus challenging. This challenge is presented by the inability of the ionising particles to penetrate the tumour body leading to their localization in the periphery as well as low doses in the tumour parenchyma. In targeted radionuclide therapy of solid tumours, the cells lying on the surface of the tumour body have the same structure and function and as a result, their destruction does not always result in the complete destruction of the tumour. Besides, the conditions inside of the tumour are hypoxic and do not permit the formation of reactive oxygen species which increases the damaging potential of the therapeutic agent. However, this problem can be addressed by the use of multi-step pre-targetted radionuclide therapy, which enhances exposure to tumour radiation and therapeutic selectivity [16].

Some of the successful applications of targetted radionuclide therapy of solid tumours include colorectal carcinoma, solid neuroendocrine malignancies, castration-resistant prostate
cancer, metastasizing melanoma, pancreatic tumour and stage-IV melanoma, amongst others. The treatment of colorectal carcinoma involves the use of I-131-conjugated anti-CEA antibodies, and it produces up to 68 months median survival time. The application of anti-PSMA antigen antibodies with Lu-177 radionuclides offer a successful treatment of castration-resistant prostate cancer produces a successful therapy with a median survival time of 10 months, while the application of anti-NG2 with Bi-213 produces a long-lasting effect in stage IV melanoma treatment. For the metastatic melanoma, the survival time increases by nine months after administration of anti-NG2 antibodies conjugated to Bi-213 radionuclide, but the application of DOTATE in conjugation with Lu-177 produces a complication-free stable disease course in 46 percent cases [17].

Advantages and disadvantages of targeted radionuclide therapy

One of the advantages of targeted radionuclide therapy is that Auger electron, alpha particle, and beta particle emitters are effective therapeutic particles as they can localize the delivery of cytotoxic ionizing radiation [18]. By linking the emitters to biological agents, localized treatment can be achieved because of the high affinity of some elements for some organs and organ systems. As a result, the therapeutic capability of these agents provides a localized killing of specific tissues and cells. Another advantage of the application of targeted radionuclides in cancer therapy is their large-scale availability [19]. Once a specific radionuclide is approved for use as a radiopharmaceutical, it becomes subject to large-scale production in the laboratory making it readily available for a wide scale application. Another advantage of targeted radionuclide therapy is a high specificity and selectivity for the target cell types [20]. Targeted radionuclides are linked to such biological components as antibodies which are specific for certain receptors expressed on cancer cells. As a result, when introduced into the body they become attached to the target cells where radionuclides decay to emit beta particles, alpha particles or Auger electrons, which kill the antibody-associated cancer cells. The mechanism leads to a selective killing of the tumour [21].

On the other hand, this therapeutic technique carries several significant disadvantages which limits its application in treating humans. One of the disadvantages of targeted radionuclide therapy is the shortage of radionuclides. For example, iodine-124, zirconium-89, astantine-89, bromine-77 and copper-67 are in short supply because of their high requirements of high-energy/complexity accelerators for production and this limits their availability in contrast to radionuclides produced by the small cyclotrons in PET centres. This limitation of radionuclide supply also limits the advancement of research and development in radiobiology and radiochemistry. Amongst those listed above, only yttrium-90 and iodine-131 are available for clinical use, but their availability is low. Another disadvantage of targeted radionuclide therapy is resistance. By being a biologically determined process, targeted radionuclide therapy is limited by resistance because some tumours might lack the receptor subtype leading to the inability to offer effective treatment. For example, a tumour may exhibit a variant subtype of somatostatin receptors leading to resistance to somatostatin-active radionuclides. Another limitation is a mutation that can lead to resistance as well. For example, mutation of somatostatin genes will result in loss of efficacy of somatostatin-targetted radionuclides [22].

Conclusion

Traditionally, radiotherapy has been utilized for cancer treatment to suppress and kill the cancerous cells. There are several disadvantages of this techniques including the unnecessary side effects and killing of the normal cells. Targeted radionuclide therapies are emerging as personalized medicine targeting only the receptor specific defective cells leading to minimize the side effect of the treatment along with maximizing the efficacy. This main advantage makes this as a treatment of choice for the patients in which it has proven benefits
benefits over the conventional treatment. We are hopeful that with upcoming research this may well be the future direction of medicine.

References


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Determination of the optimum filter for $^{99m}$Tc SPECT breast imaging using a wire mesh collimator

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Abstract

Aims The development of wire mesh collimator (WMC), has improved the performance of Single Photon Emission Computed tomography (SPECT) because of its higher sensitivity whilst maintaining the same resolution. Consequently, the WMC allows better detection of early-stage cancer. The purpose of this study was to find an optimal filter for image reconstruction for breast SPECT imaging.

Methods Half-ellipsoidal breast phantom in the prone position was simulated with dual-head SPECT camera by Monte Carlo N-Particle Transport Code, version 5 (MCNP5). Six different filters were compared with 17 different cutoff frequencies (Fc), ranging from 0.2 Nyquist frequency (Nq) to 1.0 Nq, with step 0.05. For Butterworth filter, order was from 3 to 12 with step 1. A total of 255 central slices with different parameters were reconstructed by filtered back projection (FBP) to compare the image performance in terms of contrast, noise level and tumour size.

Results The values of tumour size, contrast and noise level were greatly influenced by different filter types and the value of Fc. Ramp and Butterworth produced the best value of tumour size and contrast, whilst Parzen, Hann and Hamming filters gave smoother images. Overall, results showed that Butterworth filter with the highest mean score.

Conclusion Butterworth filter proved to be the provided the best image quality at a higher sensitivity and was found to be the optimum filter for quantitative analysis.
**Key words:** Wire mesh collimator, SPECT breast imaging, filtering, Cut-off frequency

**Introduction**

In breast SPECT imaging, projections are obtained from many angles around the breast, and then these data are reconstructed to form the tomographic images by reconstruction techniques such as filtered back projection or iterative methods. Imaging filtering is a key element of image reconstruction process and is intimately related to optimum image quality. A well-known filter, named as Ramp filter, is a type of a high-pass filter that reduce the 1/r blurring effect and preserves high frequencies, while filters like Parzen, Hann, Hamming, Shepp-logan, and Butterworth are all low-pass filters, which act as a function window that can preserve low-frequency structures and diminishing high-frequency noise [1,2]. Typical filters commonly used in commercial software package are the product of ramp and one of the five low-pass filters, as shown in Figure 1.

WMC is a newly designed collimator to replace the conventional low-energy high-resolution (LEHR) parallel-hole collimators on gamma cameras. Previously, this collimator had only been tested for 2D planar imaging of breast cancers [3-6]. There are multiple reports of SPECT imaging of breast cancers in the literature [7-10]. However, none of the studies have investigated the characteristics of the filter techniques during image reconstruction process. The choice of filter is usually a compromise between the noise and fine detail suppression of the image area of interest. In clinical practice, several factors would affect the choice of filter [1,11], such as the number of counts, the background noise level, the organs being imaged, the energy of the isotopes, and the type of collimator. In this study, we intended to find the optimum filter for SPECT breast imaging with WMC using technetium-99m source in Monte Carlo simulation environment.

**Materials and Methods**

**Monte Carlo simulation**

The SIEMENS Symbia T camera is a dual-head SPECT camera, which consists of a removable LEHR collimator, a sodium iodide (NaI) scintillation crystal, a light guide and an array of PMT [12]. The detector is filled with NaI with density of 3.67g/cm3 and size 0.9525 cm in thickness, 53.3x38.7 cm² in area. Based on this camera, MCNP5 [13] was used to simulate the geometry structure of SPECT camera with a WMC. The WMC is a parallel and square hole type of collimator, which has 101 interchangeable layers of wire with the hole size 0.15 cm, septa size 0.02 cm and a thickness of 4 cm [6]. The geometry of SPECT camera and side view of WMC is shown in Figure 2(a). The pixel size is 0.48 cm, and a hardware zoom factor of 1.23 was applied, thus yielding a pixel size with 0.39 cm [14,15]. A Pyrex slab with a density of 1.4718 g/cm3 and thickness of 6.6 cm was used to address the issue of backscatter by modelling the backscattering effect due to the light pipe, PMTs, mu-metal magnetic shielding or other structures in a real camera [16].

![Figure 1 Six commonly used filters in SPECT image reconstruction](image-url)
Half-ellipsoidal breast phantom, a close approximation of the real breast was used to simulate the clinical examination for breast cancer in the prone position [5]. Based on the early stage of TNM system [17,18], a stage 1 tumour was investigated in this study and a spherical tumour located in the center of breast phantom with diameter 1.5 cm was simulated.

In order to make the simulation approximately close to the real situation, the activity of breast should be assigned properly. For breast imaging, in general a 20 mCi (740 MBq) dose of technetium-99m is injected and the patient rests for several minutes to allow thorough distribution of the radiotracer [19-22]. To approximate the activity concentration expected from volumetric breast SPECT, the activity in the breast is converted to units of µCi/mL. Many efforts had been done to measure the activities in the breast [19,22,23], and the activity was about 80 nCi/mL for breast normal tissue. This activity had also been used in other studies [3,5,24].

**Data collection**

Every projection set was acquired with 120 angles over 360 degrees with an angle step of 3° for each projection. The method to generate the projections from the MCNP5 simulation output files followed the previous study [25].

After collecting all the projections, filter was applied to the original projections. Finally, inverse radon transformation was performed to generate the cross-sectional images of the breast phantom. Figure 3 shows the overall flow chart of methodology in this study.

**Figure 2** (a) Geometry of dual-head SPECT camera with WMC as viewed by VisEd; (b) Half-ellipsoidal geometry for breast phantom

**Figure 3** Flow chart of image reconstruction in the simulation
The transaxial slices were obtained by image reconstruction using filtered back projection with matrix of 64x64, which yields a voxel size of 0.39x0.39x0.39 cm³. Images were corrected by attenuation correction based on Chang’s method [26] with a linear attenuation coefficient of 0.12-1 cm [2,11,27]. No scatter correction was applied in this study.

Filter Evaluation

Six different filters were compared with 17 different Fc, ranging from 0.2 Nq to 1.0 Nq, with step 0.05. For Butterworth filter, order was from 3 to 12 with step 1. A total of 255 central slices with different filter parameters were reconstructed to compare the performance in terms of contrast, noise level and tumour size.

![Figure 4](image.jpg)

Figure 4  Regions of tumour and background in the central slice

Tumour size was determined using full width at half maximum (FWHM) of the four directions of profiles (00, 450, 900 and 1350) in the central slice image, purple dotted lines as shown in Figure 5. Carrie et al. [28] stated the correlation between the measured full width at 25%, 35%, and 50% of the maximum intensity profiles at various breast thicknesses and true tumour diameter. Based on that, full width at 35% of the maximum was used to determine the true tumour size. The terms, contrast and noise level were calculated in the following equations:

$$C = \frac{R_o - R_b}{R_b}$$  \hspace{1cm} (1)

where, $R_o$ is the mean value in the tumour area (regions shown by yellow arrow), while $R_b$ is the mean value in the normal breast tissue (four green rectangular regions shown in Figure 4).

$$N = \frac{\sigma_b}{R_b}$$  \hspace{1cm} (2)

where $\sigma_b$ is the standard deviation of the normal breast tissue. This term also refers to coefficient of variation.

The determination of the optimum filter for SPECT breast imaging would consider the ability of each filter type in producing high contrast, low noise, and approximate tumour size. Therefore, the total grade (trade off between contrast, noise level, and tumour size) was analyzed. To calculate the total grade, the grading method used by Takavar et al. [29] was applied. For every filter, each parameter was first graded from 1 to 100 contrast and noise (1 for worst and 100 for the best), while 1 for the biggest and 100 for the nearest tumour size to the true size.

Results

Tumour size

One example of determined tumour size by different Fc of Butterworth filter with order 6 was shown in Figure 5. Low Fc smoothed the slice in a high degree so that it led to extended tumour size. As the Fc increased, spatial resolution was improved and acceptable tumour size was obtained from Fc range of 0.55Nq to...
0.8 Nq, which yielded a tumour size about 1.6 cm. Due to high level noise, the tumour size started to increase when Fc was higher than 0.8 Nq. 

As can be seen from Table 1, the nearest FWHM to real tumour size was obtained by Ramp and Butterworth filters, which was about 1.6 cm, followed by Shepp-Logan filter. The rest of the filters did not provide an approximation between the tumour size on imaging with the actual tumour size. The lower Fc we set, the bigger the tumour size obtained. Thus, the difference between maximum and minimum value of tumour size was due to value of Fc. When a very small Fc was selected, the tumour size was almost double the real size or even bigger, which did not correspond with the clinically known tumour size. In addition, Butterworth filter yielded lowest standard derivation (SD) of 0.39, which indicated the value of Fc has less effect on tumour size than the other five filters.

Contrast

Smoothing in a high degree by low Fc lost image contrast, as shown in Figure 6. the contrast was only 1.5 when Fc was 0.2 Nq. As Fc increased, slices with high contrast were obtained. Contrast was saturated at maximum value about 4.3 when Fc was bigger than 0.55 Nq.

Table 2 summarizes the contrast for six filters. Ramp filter and Butterworth almost got the highest contrast, followed by Shepp-Logan filter. The rest of the three filters, yielded a lower contrast. When a low Fc was selected,
### Table 1  Comparison of FWHM for six filters (cm)

<table>
<thead>
<tr>
<th>Value</th>
<th>Parzen</th>
<th>Hann</th>
<th>Hamming</th>
<th>Shepp-Logan</th>
<th>Ramp</th>
<th>Butterworth</th>
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<td>Maximum</td>
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<td>1.71</td>
<td>1.63</td>
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<td>1.90</td>
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<td>SD</td>
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<td>0.77</td>
<td>0.50</td>
<td>0.45</td>
<td>0.39</td>
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### Table 2  Comparison of contrast for the six filters

<table>
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<td>Maximum</td>
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<td>Mean</td>
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<td>SD</td>
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<td>0.84</td>
<td>0.77</td>
<td>0.75</td>
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### Table 3  Noise comparison for the six filters

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<th>Shepp-Logan</th>
<th>Ramp</th>
<th>Butterworth</th>
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<tr>
<td>Maximum</td>
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<td>0.21</td>
<td>0.21</td>
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<td>Minimum</td>
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<td>Mean</td>
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<td>SD</td>
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### Table 4  Summary of total score for the six filters

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<th>Hamming</th>
<th>Shepp-Logan</th>
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<td>87.29</td>
<td>91.47</td>
<td>92.55</td>
<td>93.49</td>
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<td>Minimum</td>
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<td>12.69</td>
<td>32.37</td>
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</tbody>
</table>
slice image was dramatically smoothed. As we can see, the minimum value of contrast for Parzen, Hann and Hamming filters was about 0.6, which was substantially decreased the tumour visibility. Again, Butterworth obtained the lowest value of SD.

**Noise**

Low Fc generally eliminated noise effectively and led to a smoothing of the image. However, as we can see from Figure 7, the minimum noise level was obtained at Fc 0.4 Nq other than 0.2 Nq since we calculated the SD of background to be the noise level. With higher Fc, it generated slices with a high level noise.

The noise level for six filters was shown in Table 3. Apparently Parzen, Hann and Hamming filters got smoother images. This is reasonable because they are designed to reduce noise effectively. While Shepp-Logan and Butterworth filters, especially the Ramp filter, amplified the high frequencies, which led to a little noisier image.

**Total score**

Table 4 summarizes the total score for the six filters. Butterworth filter got the highest mean score among all the six filters, because it obtained high contrast and approximate tumour size, and a little low level of noise. At the same time, Butterworth filter obtained the highest maximum value of 93.49 and smallest SD of 12.33. in other words, Butterworth filter enabled to balance the needs of high contrast, low noise, and accurate tumour size.

Figure 8 shows one sample of central slices for the six different filers. As we can see, filters such as Parzen, Hann and Hamming yielded smoother images than the other three filters, they enlarged tumour size and decreased slice contrast. Shepp-Logan, Ramp and Butterworth filters yielded similar image quality.

**Figure 8**  *Comparison of central slices obtained from six different filters with cut-off frequency at 0.45 Nq*
The optimum parameters for Butterworth filter were Fc of 0.45 Nq and Order of 6 (see Figure 9). The Nyquist frequency in this study was 1.28 cycles/cm (0.5 cycles/pixel). So the optimum Fc was 0.58 cycles/cm.

**Figure 9** Comparison of Butterworth filter at different cut-off frequencies and order

**Discussion**

Image filtering is one of the most significant factors that greatly influences the quality of clinical SPECT images. It should balance between noise removal and resolution recovery. Currently, a number of filters are available in the 3D reconstruction process. Image quality can be variously affected by filter parameters. Therefore, there is no standard for the type of the filter and the filter parameters in all types of clinical SPECT studies. To choose the optimum filter for an individual case is still a main problem in SPECT image processing.

In this study, Butterworth filter balanced image quality among the six filters. Even though the mean contrast, noise level, and tumour size obtained with the Butterworth filter were not the best, its mean total score was the highest amongst the six filters, which indicated that the Butterworth filter enabled to balance between the needs of high contrast, low noise, and accurate tumour size. This ability is significant for quantification which is greatly dependent on the image quality. The results showed a good agreement with the previous studies [29, 30], which also showed Butterworth filter to be the best amongst the common used filters for myocardial SPECT imaging. Interestingly, the optimal parameters of Butterworth were well matched with the reported study [29], which indicates that the results of this study may apply to myocardial SPECT imaging.

It is noticeable that the order of Butterworth filter has had little effect on the slice when it was bigger than value of 6. This finding was in agreement with a published study [31], which also found that there was no major difference in their influence on the Fc of 0.5 Nq or above when estimating the optimized values of Butterworth filter for the quantification of the cardiac volumes and left ventricular ejection fraction for technetium- 99m gated myocardial SPECT. Therefore, when optimizing the parameters of Butterworth filter, many studies optimized the value of Fc while fixing the value of order [11, 32-34].

**Conclusion**

The selection of an optimal filter during the FBP image reconstruction is vital for cancer detection. The Butterworth filter is suggested to be optimum for breast SPECT imaging owing to its ability to provide a high quality image.

Although an optimum Fc for Butterworth filter in the breast SPECT imaging was found to 0.45 Nq in this study, it actually depends on the image total counts and other properties of the image. Therefore, the optimum Fc need to be decided objectively not subjectively or by "trial and error" method. If parameters of Butterworth were determined subjectively, operator repeatability decreased, so parameters should be set objectively to improve repeatability.
Acknowledgement

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References


Measurement of radiation doses to occupational workers in nuclear medicine

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²Department of Medical Physics, Nuclear Medicine, Oncology and Radiotherapy Institute (NORI), Islamabad

Abstract

Aims The study aimed at measuring the external radiation doses to workers from patients who were administered radiopharmaceuticals in the nuclear medicine department. The purpose of this study was to evaluate the radiation safety procedures in the department of nuclear medicine.

Methods A total of 80 patients were randomly selected for the study. These patients were injected with either $^{99m}$Tc-pertechnetate or $^{99m}$Tc-MDP (methylene diphosphonate). The dose rate was measured in hot lab, waiting room and in the scanning room at distances of 10, 50 and 100 cm from the patient at different time intervals by using a radiation survey meter. The absorbed dose from radioactive patient to radiation workers was calculated by using RADAR software and mathematical formula from the measured dose rate.

Results The mean dose rate from thyroid scan patients at a distance of 10, 50 and 100 cm, after administration of injection was found to be 41 µSv/h, 31 µSv/h and 22 µSv/h respectively; whereas the dose rate from bone scan patients was calculated at 62 µSv/h, 31 µSv/h and 28 µSv/h. The dose rate was also measured after 15 min and 30 min in waiting and scanning room for the same patients. The mean absorbed dose to nuclear medicine occupational workers calculated both manually and using RADAR software came out to be less than 1mSv/year.

Conclusion The external doses to radiation workers were within permissible level. The results obtained in the present study are comparable to the previous studies conducted world wide. The radiation dose level to occupational workers in our nuclear medicine department does not exceed the recommended dose limits for workers.

Key words: Radiation safety, External dose rate, absorbed dose from radioactive patient

Introduction

Radionuclides are used in nuclear medicine for various kinds of diagnostic and treatment
Radiopharmaceuticals injected to patients in a specific amount for a particular test. The most commonly used radionuclide in our department are $^{99m}$Tc and $^{131}$I. It is obvious from earlier studies that external ionizing radiation exposure of nuclear medicine workers arises mostly from radioactive patients rather than the preparation and injection of radio pharmaceuticals [1]. Many researchers have measured the dose rates at different distances and time intervals from the injected patients to highlight the exposure to radiation workers [2, 3].

Radiation exposure in nuclear medicine is caused by radioactive sources and patients. Radioactive patients are a source of radiation for workers and attendants of the patient [4]. It is therefore necessary to quantify the radiation exposure from the patients to occupational workers in the nuclear medicine department. The aim of this study was to measure external radiation doses to workers due to patients who have been administered radiopharmaceuticals in the nuclear medicine department.

**Materials and Methods**

In this study, dose rate was measured from injected patients to quantify the doses to occupational workers in the nuclear medicine department. For this purpose, 80 patients (45 males, 35 females) were randomly selected. The ages of the patients ranged from 20-60 years (mean age 37.5 years).

The selected patients were divided into two groups: 1) patients who were injected with $^{99m}$Tc-pertechnetate (thyroid scan patients) and 2) bone scan patients who were administered $^{99m}$Tc-methylene disphosphonate ($^{99m}$Tc-MDP). The activity injected to each patient was measured using a radioisotope dose calibrator (Capintec CRC®-55tR) installed the hot lab of the nuclear medicine department.

The dose rate was measured by using survey meter at preselected distances and locations. The LAMSE RM1001-RD survey meter was used in the present study. It measures the radiations in energy range of 50keV to 1.3MeV, and dose rates in the range 0.1µSv/h to 2mSv/h.

The dose rate was measured in different locations at distances of 10, 50 and 100 cm from the front of the patient. The measurements were taken in three different locations in the nuclear medicine department including the hot lab, the scanning room and the injected patients waiting room. The measurements were taken at 3 different time intervals at 1-minute, 15-minute and 30-minute after injection.

The absorbed dose from radioactive patients can be calculated by using Radiation Dose Assessment Resource (RADAR) software [5]. In this study, RADAR software was used for measurement of absorbed doses from the radioactive patients.

**Results & Discussion**

In this study, the radiation exposure to occupational workers from radioactive patients was quantified by through time and distance at different locations. Occupational exposures was assessed for whole body scan and thyroid scan which are major procedures in nuclear medicine department.

**Measurement of radiation dose from thyroid and bone scan patients**

The dose rates were measured from thyroid and bone scan patients. The measured dose rates at distances of 10, 50 and 100 cm from the patient after 1, 15 and 30 minutes of injection are given in Tables 1-3.
The measured values in Table 1-3 show that the dose rates for bone scan patients are higher than dose rates from the thyroid scan patients because the average injected activity of 15.76 mCi is higher as compared to that given for thyroid scans at 4.85 mCi. The measured values also showed that the dose rates to staff from radioactive patients depends on distance. As per the inverse square law, by increasing the distance from the injected patient, the dose rate decreases inversely with the square of the distance: doubling the distance between radioactive patient and the radiation source will reduce radiation exposure by a factor of 4. Unnecessary staff exposure is avoided by maintain a safe distance from the patient.

**Table 1** Mean dose rate after 1 minute of administrated activity of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP in the Hot Lab

<table>
<thead>
<tr>
<th>Distance (cm)</th>
<th>Thyroid scan</th>
<th>Bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose rate (μSv/h) ± SD</td>
<td>Mean dose rate (μSv/h) ±SD</td>
</tr>
<tr>
<td>10</td>
<td>41.5±10.9</td>
<td>62.7±15.9</td>
</tr>
<tr>
<td>50</td>
<td>31.7±10.4</td>
<td>44.8±14.1</td>
</tr>
<tr>
<td>100</td>
<td>22.7±8.9</td>
<td>28.8±11.7</td>
</tr>
</tbody>
</table>

**Table 2** Mean dose rate after 15 minutes of administrated activity of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP in the waiting room

<table>
<thead>
<tr>
<th>Distance (cm)</th>
<th>Thyroid scan</th>
<th>Bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose rate (μSv/h) ±SD</td>
<td>Mean dose rate (μSv/h) ±SD</td>
</tr>
<tr>
<td>10</td>
<td>28.69±9.1</td>
<td>41.9±13.1</td>
</tr>
<tr>
<td>50</td>
<td>19.36±8.1</td>
<td>26.7±11.2</td>
</tr>
<tr>
<td>100</td>
<td>11.48±6.2</td>
<td>20.3±10.5</td>
</tr>
</tbody>
</table>

**Table 3** Mean dose rate after 30 minutes of administrated activity of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP in the scanning room

<table>
<thead>
<tr>
<th>Distance (cm)</th>
<th>Thyroid scan</th>
<th>Bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose rate (μSv/h) ±SD</td>
<td>Mean dose rate (μSv/h) ±SD</td>
</tr>
<tr>
<td>10</td>
<td>18.29±8.0</td>
<td>23.7±10.8</td>
</tr>
<tr>
<td>50</td>
<td>9.6±4.9</td>
<td>14.5±8.8</td>
</tr>
<tr>
<td>100</td>
<td>6.27±3.8</td>
<td>8.24±6.2</td>
</tr>
</tbody>
</table>
The absorbed dose to nuclear medicine staff after administration of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP was calculated by using RADAR software. The absorbed dose received to the nuclear medicine staff after administration of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP given in Tables 4-6.

Table 4 Absorbed doses to staff after 1 minute of administered activity of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP in the Hot Lab

| Distance (cm) | Thyroid scan | | | Bone scan |
|--------------|--------------|--------------|--------------|
| | Absorbed dose (mSv) | Absorbed dose (mSv) | Absorbed dose (mSv) |
| 10 | 0.0068 | 0.023 |
| 50 | 0.0052 | 0.0073 |
| 100 | 0.0037 | 0.0046 |

Table 5 Absorbed doses to staff after 15 minutes of administered activity of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP in the waiting room

| Distance (cm) | Thyroid scan | | | Bone scan |
|--------------|--------------|--------------|--------------|
| | Absorbed dose (mSv) | Absorbed dose (mSv) | Absorbed dose (mSv) |
| 10 | 0.060 | 0.360 |
| 50 | 0.0048 | 0.014 |
| 100 | 0.0028 | 0.005 |

Table 6 Absorbed doses to staff after 30 minutes of administered activity of $^{99m}$Tc-pertechnetate and $^{99m}$Tc-MDP in the waiting room

| Distance (cm) | Thyroid scan | | | Bone scan |
|--------------|--------------|--------------|--------------|
| | Absorbed dose (mSv) | Absorbed dose (mSv) | Absorbed dose (mSv) |
| 10 | 0.12 | 0.71 |
| 50 | 0.058 | 0.02 |
| 100 | 0.031 | 0.01 |

Absorbed dose to staff

The exposure is directly proportional to time spent near the radioactive patients and inversely proportional to the distance from radioactive patients as shown in Figures 2 and 3.
Figure 2 shows that increasing the distance from the radioactive patients, correspondingly decreases the absorbed doses. Figure 3 shows that more exposure will result as more time is spent around a radioactive source. The exposure is directly proportional to time spent near the source and activity injected to the patient. All these measurements showed that the measured doses received by workers were well below the dose limit recommended by the ICRP. The calculated dose does not exceed the recommended dose limits of 1 mSv [6]. The results showed that the radiation dose levels in the nuclear medicine department does not exceed the recommended dose limits to the workers of less than 20 mSv per annum and 1.4 mSv per month. According to ICRP, the maximum allowable dose for one day of nuclear medicine department is 55 µSv [7]. Dose limit for whole-body is 20 mSv per year, prescribed by ICRP and AERB [8, 9] for radiation workers. The measured doses received by workers were well below the dose limits recommended by the ICRP.

Conclusion

Radiation safety is of prime importance in nuclear medicine and occupational workers should be monitored regularly. In this study, it was found that external doses to radiation workers were within permissible level. The annual effective doses received by the nuclear medicine staff during whole-body scan and thyroid scan procedures were less than 1mSv/year. It is obvious that exposure to workers does not exceed to the recommended limits set by basic safety standards, published by the International Atomic Energy agency (IAEA).

References


References


7. ICRP publication 106 "Radiation Dose to Patients from Radiopharmaceuticals". (2007).


Behaviour of wedges for different field sizes and depths

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Abstract

Aims The relative dosimetry plays vital part in treatment planning of patients. Factors such as percent depth doses, tissue maximum ratios, tray factors, wedge factors, etc., determined from the relative dosimetry, affects the patient dose. The current study intended at measuring and evaluating the wedge factor for different field sizes and depths for $^{60}$Co teletherapy unit GWXJ80 of NPIC China.

Methods The measurements for 15°, 30°, 45° and 60° wedges for different field sizes and depths on $^{60}$Co teletherapy unit GWXJ80 of NPIC China installed at Nuclear Institute of Medicine and Radiotherapy (NIMRA), Jamshoro, Pakistan, were done in water phantom of 30x30x30 cm$^3$ dimension at 80 cm Source-to-Surface Distance (SSD) by using calibrated Farmer’s NE 2570 electrometer with NE 2571 0.6 cc ionization chamber.

Results The evaluation of data showed that there was no significant difference in factor of each of wedge being analyzed for different field sizes and depths.

Conclusion We The current study suggests that wedge factor for a particular wedge is approximately a constant value irrespective of field size and depth. The measurement for only one field size at one depth is sufficient to calculate the wedge factor for a particular wedge.

Key words: $^{60}$Co, Quality assurance, Relative dosimetry, Field size, Depth.

Introduction

In radiotherapy, absolute dosimetry or simply dosimetry, is a systemic procedure for measuring the absorbed dose (also termed as calibration) in unit of Gy (Gray) of teletherapy machine directly under reference conditions (same field size at same depth with constant gantry and collimator angles and at a fixed SSD). All further measurements are then compared to this known dose under specific conditions termed as relative dosimetry [1]. From these relative dosimetry variables, wedge filters are one of beam modifying devices and are being used to optimize the dose distribution in patients' target tissues [2-5]. Due to the presence of wedge filter in the path of radiation beam, attenuation occurs in the beam intensity which can be expressed

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in the form of wedge factor (WF) at the central axis of the radiation beam [2, 4]. This attenuation is taken into consideration for calculating the patient dose and treatment time (TT) or monitor units (MU) [4-6].

Most of the times single WF is used for the patients’ TT or MUs, with usually measurements made for the reference field size of $10 \times 10 \text{ cm}^2$ at reference depth of $d_{\text{max}}$ or $d_5$ or $d_{10}$ [3]. Various researchers [2-32] have conducted studies on wedge factors for LA (Linear Accelerator), $^{60}$Co (cobalt-60) or for both type of treatment machines (LA, $^{60}$Co) as summarized in Table 1. As seen from Table 1, several studies [2, 3, 6-23] have been conducted for LA only, whereas other studies [24-27] for both (LA and $^{60}$Co) and still other studies [4, 5, 28-32] for $^{60}$Co only. This study aimed at computing and comparing the differences in WFs of different wedges for different field sizes at different depths.

**Material and Methods**

The WF of different wedge angles ($15^\circ$, $30^\circ$, $45^\circ$ and $60^\circ$) on different field sizes at depths of 0.5 and 10 cm were studied for GWXJ80 of NPIC China installed at Nuclear Institute of Medicine and Radiotherapy (NIMRA) Jamshoro Pakistan were done in water phantom with $30\times30\times30 \text{ cm}^3$ dimension at $80 \text{ cm}$ Source to Surface Distance (SSD) using calibrated NE 2570 Farmer Electrometer and 0.6 cc Farmer ionization chamber NE 2571. All of the measurements were performed at $0^\circ$ gantry and collimator angles [33, 34]. The setups for non-wedged and wedged beams are shown in Figures 1 and 2.

The calculation of WF for a specific field size at particular depth in water phantom was done by using the formula:

$$WF = \frac{\text{Dose measured with wedge filter}}{\text{Dose measured for open beam or without wedge filter}}$$

The measurement for specific wedge is to be one at same set of parameters (like for same field size at same depth, for the same dose or time of exposure with constant gantry and collimator angles and at fixed SSD [2, 27, 33, 34].
Table 1 List of various studies done on wedge factor for LA only, $^{60}$Co only or for both (LA and $^{60}$Co) along with dependant factors (Field Size, Depth, SSD)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Study</th>
<th>Modality LA/ Both (LA and $^{60}$Co)</th>
<th>Factor dependency (FS, Depth, SSD/Dist.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saffar MH et al. [2]</td>
<td>LA</td>
<td>Field Size, Depth, SSD</td>
</tr>
<tr>
<td>2</td>
<td>Ahmad M et al. [3]</td>
<td>LA</td>
<td>Field Size, Depth</td>
</tr>
<tr>
<td>3</td>
<td>Popescu A et al. [6]</td>
<td>LA</td>
<td>Field Size, Depth, SSD</td>
</tr>
<tr>
<td>4</td>
<td>Bar-Deroma RD and Bjärngard BE [7]</td>
<td>LA</td>
<td>Field Size, Depth</td>
</tr>
<tr>
<td>5</td>
<td>Podgorsak MB et al. [8]</td>
<td>LA</td>
<td>Field Size, Depth</td>
</tr>
<tr>
<td>6</td>
<td>Popple RA et al. [9]</td>
<td>LA</td>
<td>Field Size</td>
</tr>
<tr>
<td>7</td>
<td>Sewchand W et al. [10]</td>
<td>LA</td>
<td>Field Size, Depth</td>
</tr>
<tr>
<td>8</td>
<td>Palta JR et al. [11]</td>
<td>LA</td>
<td>Field Size</td>
</tr>
<tr>
<td>9</td>
<td>Wu A et al. [12]</td>
<td>LA</td>
<td>Field Size</td>
</tr>
<tr>
<td>10</td>
<td>McCullough EC et al. [13]</td>
<td>LA</td>
<td>Depth</td>
</tr>
<tr>
<td>11</td>
<td>Liu C et al. [14]</td>
<td>LA</td>
<td>Field Size</td>
</tr>
<tr>
<td>12</td>
<td>Zhu XR et al. [15]</td>
<td>LA</td>
<td>Field Size, Depth</td>
</tr>
<tr>
<td>13</td>
<td>Van Santvoort J [16]</td>
<td>LA</td>
<td>Not Available</td>
</tr>
<tr>
<td>14</td>
<td>Wichman BD [17]</td>
<td>Both (LA and $^{60}$Co)</td>
<td>Field Size, Depth</td>
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<td>15</td>
<td>Gibbons JP [18]</td>
<td>Both (LA and $^{60}$Co)</td>
<td>Field Size and Depth</td>
</tr>
<tr>
<td>16</td>
<td>Cozzi FA et al. [19]</td>
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<td>Field Size, Depth</td>
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<tr>
<td>17</td>
<td>Dean EM and Davis JB [20]</td>
<td>Both (LA and $^{60}$Co)</td>
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<td>18</td>
<td>Thomas J [21]</td>
<td>Both (LA and $^{60}$Co)</td>
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<td>19</td>
<td>Birgani MJT [22]</td>
<td>Both (LA and $^{60}$Co)</td>
<td>Field Size, Depth</td>
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<td>20</td>
<td>Choi DR et al. [23]</td>
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<td>Field Size</td>
</tr>
<tr>
<td>21</td>
<td>Niroomand-Rad A et al. [24]</td>
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<td>Field Size, Depth</td>
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<tr>
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<td>Heukelom S et al. [25]</td>
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<td>23</td>
<td>Kalend AM et al. [26]</td>
<td>Both (LA and $^{60}$Co)</td>
<td>Field Size, Depth</td>
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<tr>
<td>24</td>
<td>Tailor RC et al. [27]</td>
<td>Both (LA and $^{60}$Co)</td>
<td>Field Size, Depth</td>
</tr>
<tr>
<td>25</td>
<td>Haq M M et al. [4]</td>
<td>$^{60}$Co</td>
<td>Field Size, Depth, SSD</td>
</tr>
<tr>
<td>26</td>
<td>Safar MH et al. [5]</td>
<td>$^{60}$Co</td>
<td>Field Size</td>
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<td>27</td>
<td>Kinhikar RA et al. [28]</td>
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</tr>
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<td>28</td>
<td>Andrabji WH et al. [29]</td>
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<td>Not Available</td>
</tr>
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<td>29</td>
<td>Akinlade BI et al. [30]</td>
<td>$^{60}$Co</td>
<td>Not Available</td>
</tr>
<tr>
<td>30</td>
<td>Malik SR et al. [31]</td>
<td>$^{60}$Co</td>
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</tr>
<tr>
<td>31</td>
<td>Tagoe SNA et al. [32]</td>
<td>$^{60}$Co</td>
<td>SSD</td>
</tr>
</tbody>
</table>

Results

The WF for different field sizes at different depths (05 and 10 cm) along with their means and standard deviations (SD) for $^{60}$Co teletherapy unit GWXJ80 of NPIC China installed at Nuclear Institute of Medicine and Radiotherapy (NIMRA) Jamshoro Pakistan have been congregated into in Tables 2 and 3 whereas their graphical representation have been shown in Figures 3 to 6.

Discussion

The results from other researchers on wedge factors for LA, $^{60}$Co or for both type of treatment machines (LA, $^{60}$Co) along with current study on $^{60}$Co teletherapy machines
Table 2  Wedge Factor of different wedge angles for different field sizes at 05 cm depth with their mean and standard deviation

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Wedge Angle</th>
<th>Wedge Identification</th>
<th>Field Size cm x cm</th>
<th>Wedge Factor 05 cm</th>
<th>Mean</th>
<th>Standard Deviation</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>15°</td>
<td>W15</td>
<td>5 x 5</td>
<td>0.691011236</td>
<td>0.695123403</td>
<td>0.004542877</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.694358974</td>
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<td></td>
<td>10 x 15</td>
<td>0.700000000</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>30°</td>
<td>W30</td>
<td>5 x 5</td>
<td>0.573033708</td>
<td>0.576481321</td>
<td>0.003483690</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>10 x 10</td>
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<tr>
<td>3</td>
<td>45°</td>
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<td>0.597752809</td>
<td>0.600601364</td>
<td>0.002467054</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.602051282</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 15</td>
<td>0.602000000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60°</td>
<td>W60</td>
<td>5 x 5</td>
<td>0.440449438</td>
<td>0.446153846</td>
<td>0.008952596</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.446153846</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 15</td>
<td>0.458000000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3  Wedge Factor of different wedge angles for different field sizes at 10 cm depth with their mean and standard deviation

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Wedge Angle</th>
<th>Wedge Identification</th>
<th>Field Size cm x cm</th>
<th>Wedge Factor 10 cm</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15°</td>
<td>W15</td>
<td>5 x 5</td>
<td>0.693251534</td>
<td>0.695602077</td>
<td>0.002179005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.696000000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 15</td>
<td>0.697554698</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30°</td>
<td>W30</td>
<td>5 x 5</td>
<td>0.582822086</td>
<td>0.582404445</td>
<td>0.000593885</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.582666667</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 15</td>
<td>0.581724582</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45°</td>
<td>W45</td>
<td>5 x 5</td>
<td>0.605828221</td>
<td>0.606653165</td>
<td>0.000818277</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.606666667</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 15</td>
<td>0.607464607</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>60°</td>
<td>W60</td>
<td>5 x 5</td>
<td>0.447852761</td>
<td>0.453579406</td>
<td>0.004979142</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 10</td>
<td>0.456000000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 x 15</td>
<td>0.456885457</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4  Wedge Factor from different researchers including current study with modality (for LA only, 60Co only or for both (LA and 60Co)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Study</th>
<th>Modality</th>
<th>WF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LA/ Both</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Hajizadeh SM et al. [2]</td>
<td>LA/Both (LA and 60Co)</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>2</td>
<td>Ahmad M et al. [3]</td>
<td></td>
<td>&lt;10%</td>
</tr>
<tr>
<td>3</td>
<td>Popescu A et al. [6]</td>
<td></td>
<td>&lt;±1.0%</td>
</tr>
<tr>
<td>4</td>
<td>Bar-Deroma RD and Bjärngard BE [7]</td>
<td></td>
<td>&lt;±1.5%</td>
</tr>
<tr>
<td>5</td>
<td>Podgorsak MB et al. [8]</td>
<td></td>
<td>&lt;25%</td>
</tr>
<tr>
<td>6</td>
<td>Popple RA et al. [9]</td>
<td></td>
<td>&lt;2%</td>
</tr>
<tr>
<td>7</td>
<td>Palta JR et al. [11]</td>
<td></td>
<td>(3.5-7)%</td>
</tr>
<tr>
<td>8</td>
<td>McCullough EC et al. [13]</td>
<td></td>
<td>(2-5)%</td>
</tr>
<tr>
<td>9</td>
<td>Liu C et al. [14]</td>
<td></td>
<td>&lt;1%</td>
</tr>
<tr>
<td>10</td>
<td>Van Santvoort J. [16]</td>
<td></td>
<td>&lt;3.5%</td>
</tr>
<tr>
<td>11</td>
<td>Wichman BD. [17]</td>
<td></td>
<td>(1-3)%</td>
</tr>
<tr>
<td>12</td>
<td>Gibbons JP. [18]</td>
<td></td>
<td>(1-4)%</td>
</tr>
<tr>
<td>13</td>
<td>Cozzi FA et al. [19]</td>
<td></td>
<td>&lt;1.5%</td>
</tr>
<tr>
<td>14</td>
<td>Birgani MJT [22]</td>
<td></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>15</td>
<td>Choi DR et al. [23]</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>16</td>
<td>Heukelom S. et al. [25]</td>
<td></td>
<td>&lt;9%</td>
</tr>
<tr>
<td>17</td>
<td>Tailor RC et al. [27]</td>
<td></td>
<td>(2-5)%</td>
</tr>
<tr>
<td>18</td>
<td>Haq MM et al. [4]</td>
<td>60Co</td>
<td>&lt;3.5%</td>
</tr>
<tr>
<td>19</td>
<td>Safar MH et al, [5]</td>
<td></td>
<td>&lt;1%</td>
</tr>
<tr>
<td>20</td>
<td>Kinhikar RA et al. [28]</td>
<td></td>
<td>&lt;2%</td>
</tr>
<tr>
<td>21</td>
<td>Andrali WH. Et al. [29]</td>
<td></td>
<td>&lt;2%</td>
</tr>
<tr>
<td>22</td>
<td>Akinlade BI et al. [30]</td>
<td></td>
<td>&lt;5.5%</td>
</tr>
<tr>
<td>23</td>
<td>Malik SR et al. [31]</td>
<td></td>
<td>&lt;1%</td>
</tr>
<tr>
<td>24</td>
<td>Tagoe SNA et al. [32]</td>
<td></td>
<td>&lt;±0.50%</td>
</tr>
<tr>
<td>25</td>
<td>Current Study</td>
<td></td>
<td>&lt;±2.5%</td>
</tr>
</tbody>
</table>

[2-9, 11,13, 14, 16-19, 22,23,25, 27-32] has been summarized in Table 4. As seen in the table 4, studies [2, 3, 6-9, 11, 13, 14, 16-19, 22] shows WF for LA only, whereas studies [23, 25, 27] shows factor for both (LA and 60Co) and studies [4, 5, 28-32] for 60Co only. For LA, the WF differed is between 1% to 25%, whereas for both (LA and 60Co) and for 60Co only including current study, the difference in WFs is between 2%-9% and 0.5%-5.5% respectively.

The current study is comparable and judged to other studies done for WF for 60Co only or with all other data available for LA, or for both (LA and 60Co). Most of the available data (specially for 60Co only) did not show any significant influence on the Wedge factor [2, 16].

Small negligible variations within about ±2.5% for most of WF have been observed which can affect little bit on dose of the patient. The overall error in dose delivery to patients should not go beyond to ±5% [33] on recommendations of reports of International Commission on Radiation Units and Measurements (ICRU) [35, 36] and the Nordic Association Of Clinical Physicists (NACO) [37].
Figure 3 Graphical representation of wedge factors for different wedges for different field sizes at 05 cm depth

Figure 4 Graphical representation of wedge factors for different wedges for different field sizes at 10 cm depth
Figure 5 Graphical representation of mean Wedge Factors for different wedges at 05 and 10 cm depths

Figure 5 Graphical representation of Wedge Factors for different wedges for different field sizes at 05 and 10 cm depths
Conclusion

The current study presents a comparison of WF for Wedges supplied with the teletherapy unit. The data evaluation showed that non significant difference in WF of each of wedge being analyzed for different field sizes at different depths. This study suggested that WF for a specific wedge is approximately a constant ratio irrespective of field size and depth. The measurement for only one field size at one depth is adequate to calculate the WF for a specific wedge.

Acknowledgement

The authors wish to thank Mr. Wajid Hussain PT and Mr. Abdul Qadeer SSA for their assistance and helping in taking measurements on teletherapy machine, without their help the current study cannot be successfully completed.

References


Pre-operative cardiac risk stratification for non-cardiac surgery in cancer patients using myocardial perfusion scintigraphy

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2Department of Basic Health Sciences, College of Medicine, Princess Noura Binta Abdulrehman University for Women, Riyadh, KSA
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4Department of Chemistry, Pavia University, Italy

Abstract

Aims Cancer patients are at a higher risk for any cardiac event during and post surgery, due to an altered coagulation state and anaemia, and can have additive effect if the patient had previous history of any cardiac event or risk factor for coronary artery disease such as hypertension and diabetes. The objective of this study was evaluate the usefulness of gated myocardial perfusion scintigraphy with pharmacological stress in determining the frequency of cardiac events associated with non-cardiac surgery in cancer patients.

Methods 100 consecutive patients, who were being planned for the oncological surgery, were enrolled in this study for preoperative gated myocardial perfusion scintigraphy using 99mTc-sestamibi with adenosine stress. After acquiring the data, perfusion images were reconstructed and analysed using visual assessment as well as QPS program and summed stress score (SSS) was obtained. Based on visual assessment and SSS, we divided patients into low- and high-risk groups. Postoperative follow-up of the patients was done through internal medicine clinics.

Results Out of 100 patients, 57 were female and 43 male with a mean age 61.25 years. Sixty-three (63%) had a history of diabetes, 73% hypertension, 34% were known smokers while 42% had a family history of coronary artery disease and 15 patients has CAD. 61% fell into the low-risk group and thirty-nine (39%) in the high-risk group. In the low-risk
1 patient (1.63%) needed inotropic support postoperatively. In the high-risk group, 6 (15.38%) patients had cardiac events postoperatively. Subset-analysis of these showed; 3 (7.69%) had an episode of angina prior to discharge, 2 (5.12%) died with cardiac-arrest due to myocardial infarction (MI) and 1 (2.56%) needed inotropic support postoperatively and surgery was deferred in 4 patients due to their very low LVEF and high SSS. These 4 patients were further evaluated by cardiologist for future management.

**Conclusion**  In low-risk group patients, stress myocardial perfusion scintigraphy has a high negative predictive value for peri- and post-operative cardiac events in cancer patients. While patients with cancer and labelled as high-risk on myocardial perfusion imaging, whether demonstrating scar or ischaemia, should prompt appropriate peri- and post-operative management to minimize major cardiac events.

**Key words:** Myocardial perfusion scintigraphy, Pre-operative risk assessment, $^{99m}$Tc-sestamibi, Pharmacological stress, Adenosine, Coronary artery disease

**Introduction**

Coronary artery disease (CAD) is the leading cause of death with no limitation to geographic boundaries accounting for about 16.7 million deaths worldwide [1]. Cancer by itself is associated with coagulation disorders due to hypercoagulable state and can cause coronary thromboemboli. However, there is no definite evidence that cancer by itself or any particular tumour type predisposes to coronary atherosclerosis [2]. No single test can diagnose or stratify the risk of having CAD. The evidence that myocardial perfusion imaging (MPI), has a strong prognostic value, is overwhelming [3] because of its higher diagnostic sensitivity and specificity than exercise electrocardiography (80% and 92% vs. 64% and 82% respectively) for coronary artery disease [4]. MPI is also used for assessing the functional importance of known coronary stenoses risk stratification before major non-cardiac surgery [5].

Gated stress MPS is the most commonly used and well documented noninvasive method for risk stratification. It is most cost-effective in patients with a clinically intermediate risk of a subsequent cardiac event [6]. According to ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery in patients with known CAD or the new onset of signs or symptoms suggestive of CAD, baseline cardiac assessment should be performed [7].

The surgery-specific cardiac risk of non-cardiac surgery is related to two important factors. First, the type of surgery by itself, and second, the likelihood of underlying heart disease. Pharmacologic testing with MIBI SPECT has been used to assess risk of future cardiac events in patients in a stable condition unable to perform an exercise test. An abnormal MIBI study is reported to be the strongest independent predictor of increased risk of nonfatal MI or cardiac death (odds ratio, 10.0; 95% CI, 2.3 to 43.0) [8]. Several studies have assessed the perioperative and long-term prognostic value of dipyridamole MIBI imaging in vascular surgery patients. Literature review suggests that dipyridamole, adenosine, and dobutamine testing with MIBI imaging may be effective for perioperative and long-term risk stratification in some patients undergoing non-cardiac surgery [9]. However, more studies are needed to better define which patients may benefit from testing based on clinical risk factors and type of surgery etc.

The purpose of this study was to evaluate the usefulness of gated myocardial perfusion scintigraphy (G-SPECT) with Adenosine pharmacological stress for determining the frequency of cardiac event associated with non-cardiac surgery in cancer patients.

**Methods**

We conducted a cross sectional observational study at our department. We included 100 cancer patients fulfilling the inclusion criteria
Table 1  Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Advance age of more than 40 years</td>
</tr>
<tr>
<td>2. Either sex (male and female)</td>
</tr>
<tr>
<td>In addition, one or more than one of the following:</td>
</tr>
<tr>
<td>- Abnormal ECG (Left ventricular hypertrophy, LBBB, ST abnormalities)</td>
</tr>
<tr>
<td>- Rhythm other than sinus (e.g. atrial fibrillation)</td>
</tr>
<tr>
<td>- Low functional capacity (e.g. inability to climb one flight of stairs)</td>
</tr>
<tr>
<td>- History of stroke</td>
</tr>
<tr>
<td>- Known case of systemic hypertension and on medication</td>
</tr>
<tr>
<td>- Mild angina pectoris (Canadian class I or II)</td>
</tr>
<tr>
<td>- Prior myocardial infarction by history or pathological Q waves</td>
</tr>
<tr>
<td>- Compensated or prior congestive heart failure</td>
</tr>
<tr>
<td>- Known case of diabetes mellitus</td>
</tr>
<tr>
<td>- Unstable coronary syndrome including acute myocardial infarction</td>
</tr>
<tr>
<td>- Unstable or severe angina (Canadian class III or IV)</td>
</tr>
<tr>
<td>- Decompensate congestive heart failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Previous history of surgery</td>
</tr>
<tr>
<td>2. Post chemotherapy</td>
</tr>
<tr>
<td>3. Pregnancy</td>
</tr>
<tr>
<td>4. High grade atrioventricular block</td>
</tr>
<tr>
<td>5. Symptomatic ventricular arrhythmias</td>
</tr>
<tr>
<td>6. Supraventricular arrhythmias</td>
</tr>
<tr>
<td>7. Severe valvular disease</td>
</tr>
</tbody>
</table>

(Table 1), who were referred from the medicine and anesthesia departments of SKMCH & RC for preoperative cardiac risk stratification. The patients were advised to fast for 4 hours, with no caffeine for at least 12 hours prior to study. After giving informed consent, the patients underwent gated myocardial perfusion scintigraphy prior to surgery as two-day protocol. On the first day, stress myocardial scintigraphy was performed using adenosine infused over 6 minutes in a dose of 140 µg per kg body weight per minute for pharmacological stress. $^{99m}$Technetium-2-methoxyisobutylisonitrile ($^{99m}$Tc-sestamibi) was injected 3 minutes after starting the adenosine infusion. Patient was advised to take fatty meal at 20 minutes post injection and gated single-photon emission computed tomography (G-SPECT) was performed 45-60 minutes postinjection by using a dual-headed gamma camera with SPECT capability. Images were obtained by using low-energy high-
high-resolution collimators. Energy window 20% was centered at 140 keV with matrix size of 64 X 64.

SPECT was obtained by step and shoot method, 180° of motion arc, 45° right anterior oblique (RAO) to 135° left posterior oblique (LPO) with 32 projections, each of 30-second duration per projection, 8 frame per projection. Gated SPECT was obtained by ECG synchronized data collection. Images were reconstructed by using QPS/QGS software.

Stress and rest scan images was sliced into three planes: short axis (SA), horizontal long axis (HLA) and vertical long axis (VLA). Polar map (bull’s eye) was used for quantitative perfusion defects analysis and 20-segment summed stress score (SSS) was calculated.

If there was evidence of a perfusion defect in stress scintigraphy, the patient was called in for rest scintigraphy the next day. Both the stress and the rest images were processed together to see evidence of reperfusion. Post scintigraphy risk stratification was mentioned in the report on the basis of 20-segment summed stress score (SSS).

The patient was followed up and observed for any cardiac related event (e.g., cardiac death, myocardial ischaemia, heart failure, fatal arrhythmia, unstable angina, etc.) peri and post operatively up to 2 weeks, and these were documented.

Statistical Analysis

The data analysis was carried out using computer based Statistical Package for Social Sciences (SPSS) version 14. Quantitative variables such as age and qualitative variables such as sex (male/female), diabetes, hypertension, body mass index, LVEF > 55% and final conclusion, i.e. per-operative cardiac event (Yes/No) and post-operative cardiac event (Yes/No) was presented by calculating the frequency and percentage. Correlation of any cardiac event (peri- and post-operatively) was made with the post-scintigraphic risk stratification.

Results

Out of 100 patients, 43 were male and 57 female with ages ranging from 41-88 years with a the mean age of 61.25 years. Thirty-eight patients were operated on for breast cancer, 10 for colon cancer, 8 for lung cancer, 6 stomach cancer, 5 for oesophageal cancer, 5 for renal cell carcinoma (RCC), 4 for hepatocellular cancer (HCC), and 24 for other cancers which included cervical, ovarian, tongue, pancreatic and thyroid cancers.

Sixty-three percent of that patients had a history of diabetes, 73% were hypertensive, 34% were known smokers whilst 42% had family history of coronary artery disease and 15% patients has CAD, 59% had body mass index (BMI) more than 25 while 41% had BMI less than 25.

Following data acquisition, QPS software was used for quantitative analysis including calculation of summed stress score (SSS). Out of total 100 patients, 61 had a SSS ≤ 4 (Figure 1), which was considered as normal while 39 had SSS ≥ 5 (Figure 2). On subset analysis of these 39 patients, 15 had SSS between 5-8, which was considered as mildly abnormal, 20 patient had SSS between 9-13 which was considered as moderately abnormal and 4 patients had SSS more than 13 which was considered as severely abnormal. On the same stress MPI, QGS software was used to calculate the left ventricular ejection fraction (LVEF). Minimum LVEF was 22% and maximum LVEF was 87%. 18 out of 100 patients had LVEF less than 55%. On the basis of SSS and LVEF out of 100, 39 patients fell into high-risk group for peri- and post-operative cardiac events while 61 patients were assigned in to the low-risk group for cardiac events. On subset analysis of low-risk group, only one patient out of 61 patients (1.63%) needed inotropic support post operatively (Figure 3). This patient had SSS of 3 and a LVEF 49% on MPI. The patient was a 73-year-old male with risk factors for CAD including diabetes, hypertension, smoking with positive family history for CAD but no previous history of CAD.
In the high-risk group, 6 (15%) patients had adverse cardiac events postoperatively and surgery was deferred in 4 (10%) patients (Figure 4). Subset-analysis of these showed: 3 (7.69%) had an episode of angina prior to discharge, 2 (5.12%) died with cardiac-arrest and 1 (2.56%) needed inotropic support post-operatively (Figure 5). Four patients in whom surgery deferred were further evaluated by cardiologists for future management. All of these 4 patients fell into moderately to severely abnormal category according to their SSS; out of these, one patient had an SSS in the range of 9-13 whilst the rest of the 3 patients has SSS more than 13. All these patients also had a very low LVEF at 22%, 26%, 46% and 29% respectively. On visual analysis these 4 patients has moderate to large size fixed perfusion defects indicating old myocardial infarction.

Discussion

Patients undergoing major non-cardiac surgery have a significant risk of cardiovascular morbidity and mortality [10]. Although the peri- and post-operative event rate has declined over the past 30 years as a consequence of recent developments in the
anaesthesiology and surgical techniques (e.g., regional anaesthesia and endovascular treatment modalities), peri- and post-operative cardiac complications remain a significant problem. A pooled analysis of several large studies found a 30-day incidence of cardiac events (peri- and post-operative myocardial infarction or cardiac death) of 2.5% in unselected patients over the age of 40 years [11, 15]. These complications were higher in vascular surgery patients, who had an incidence of 6.2% for cardiac events [12]. The risk of peri- and post-operative cardiac complications is the summation of the individual patient's risk and cardiac stress related to the surgical procedure.

The first step in pre-operative care is an adequate identification of patients at risk for peri- and post-operative cardiac events. In the past decades, several risk indices have been developed in this context to stratify surgical patients including introduction of Bayesian approach using pre-test probabilities in 1986, which was later modified by Lee et al. in 1999 [13]. This Revised Cardiac Risk Index, is currently the most widely used model of risk assessment in non-cardiac surgery. This index identifies 6 predictors of major cardiac complications including: 1) high-risk surgery, 2) ischaemic heart disease, 3) congestive heart failure, 4) cerebrovascular disease, 5) insulin-dependent diabetes mellitus, and 6) renal failure.

When the pre-operative risk assessment indicates an increased cardiac peri- or post-operative risk, further cardiac testing is warranted [13]. The predominant theme of testing is the impact of test results on peri- and post-operative management: if test results will not influence management, testing is not recommended. According to the 2007 guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA), patients with active cardiac conditions (i.e., unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease) have to be evaluated and treated before surgery [14]. Pre-operative cardiac testing for elective surgery is reasonable for patients with intermediate to high clinical risk factors and poor functional capacity who require vascular surgery. Pre-operative testing may be considered in patients with at least 1 to 2 or more clinically known risk factors and poor functional capacity undergoing for non-cardiac surgery [15].

Noninvasive testing is not recommended for patients without clinical risk factors undergoing intermediate or low-risk non-cardiac surgery. Several noninvasive tests are available for peri- and post-operative risk assessment. The most commonly used stress test for detecting myocardial ischaemia is the treadmill or cycle ergometer test. These tests provide an estimate of the functional capacity and haemodynamic response and detect myocardial ischaemia by ST-segment changes. The accuracy varies widely among studies [16]. However, an important limitation in patients undergoing non-cardiac surgery is the frequently limited exercise capacity in the elderly and the presence of claudication, arthritis, or chronic obstructive pulmonary disease. Consequently, non-physiologic stress tests, such as dobutamine stress echocardiography or dipyridamole or adenosine myocardial perfusion scintigraphy (MPS), are recommended in patients with limited exercise capacity [17, 24].
Myocardial perfusion scintigraphy is a widely used imaging technique for pre-operative evaluation. This technique involves intravenous administration of a small quantity of a radioactive tracer such as a technetium-99m labelled radiopharmaceutical. Images are obtained at rest and during vasodilator stress [18]. Detection of CAD is based on a difference in blood flow distribution during vasodilator stress induced by insufficient coronary blood flow increment attributed to coronary stenosis. A positive MPS is associated with increased risk of peri- and post-operative cardiac complications. Studies indicate that MPS is highly sensitive for prediction of cardiac complications, but the specificity has been reported to be less satisfactory [19, 23].

From the results of our study, those patients who have intermediate to high pre-test probability for CAD, are considered the best candidates for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI). In patients with normal stress 99mTc-sestamibi SPECT, MPI is associated with a very low risk of a cardiac event, as in our study it is only 1.63% while in literature it is 0.6% annually [20, 25].

Patients in the high-risk group according to summed stress score on MPI were further divided into 3 groups including mildly abnormal, moderately abnormal and severely abnormal risk groups. Surgery was deferred in all 4 patients who fall in severely abnormal group according to SSS and lower than the normal LVEF, and these patients were referred to a cardiologist for further evaluation and treatment according to the guidelines. Amongst the patients in the sub group of mild to moderately abnormal SSS on MPI, a cardiac event occurred in 6 (15.38%) patients only. Two (5.12%) patients had death due to myocardial infarction (MI) while 3(7.69%) had episode of chest pain without a rise in troponin I though this percentage of cardiac event is slightly higher than what the literature quotes, i.e about 6% (21,22) but we should not forget that all of these 6 patients were high-risk cancer patients with multiple known risk factors for CAD and all of them underwent high-risk non-cardiac surgery. This kind of surgery by itself carries a high mortality and morbidity per operatively due to prolonged anesthesia and surgery time and postoperatively due to prolonged bed rest.

Our study has some limitations including: 1) small sample size, 2) sampling is non-probability; purposive so the results cannot be generalized and does not represent the entire cancer population; and 3) ideally Summed Rest Score (SRS) and Summed Difference Score (SDS) should also be calculated on the rest perfusion imaging in those patients in whom the stress MPI turned out to be abnormal.

Conclusion

Stress MPI provides incremental diagnostic and prognostic value in patients at an intermediate or high pretest likelihood of CAD or patients with known risk factors for CAD. Patients who exhibit normal myocardial perfusion and function or have a small defect with normal left ventricular function have less likelihood of any adverse cardiac event peri- and post-operatively; however, patients with cancer and labelled as high-risk on myocardial perfusion imaging, whether demonstrating scar or ischaemia, should have prompt and appropriate peri- and post-operative management to minimize major cardiac events.

References


Clinical characteristics and long-term outcome of patients with differentiated carcinoma of thyroid with bone metastases: a retrospective study

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Abstract

Aims Bone is the second most frequent target of distant metastases in patients with differentiated thyroid cancer (DTC). However, there is a controversy regarding the long-term outcome of the breast cancer patients with bone metastases. This study therefore was designed with the objective of assessing the clinical characteristics related to the long-term outcome and prognosis of patients with bone metastases.

Methods We reviewed the medical records of 360 patients of differentiated thyroid cancer followed at our institute from 2007 to 2012. A total of 57 patients were found to have bone metastases, who we analyzed with regard to their basic demographic data, clinical characteristics, treatment and clinical outcomes.

Results The incidence of bone metastases from thyroid carcinoma was 15.8%. The mean age at the diagnosis of bone metastases was 47±18 years (range 16 to 80 years); 46% patients were below 40 years of age and 53.8% of the patients were above 40 years of age. 15.3% were males and 84.6% were females. Histopathologic subtypes included papillary (38%), and follicular (45.6%). Multiple bone sites were involved in 50% of the patients with 29% of the patients with single bone site involvement; and 20.8% of the patients had metastases to other body organs. All patients underwent near-total thyroidectomy followed by aggressive radioiodine therapy. Number of 131I doses received ranged from 3 to 12 with a mean of 6.6. Mean dose of 131I per patient was 48914 MBq ± 20424 (Range: 18130 - 76960). Baseline thyroglobulin (TG) level ranged from 380ng/ml to 17300ng/ml with a mean value of 2250±5644 ng/ml. 60% of the patients showed a declining trend in TG over time, whilst 23% of the patients showed a rising trend; 6.2% of the patients had normal TG/ATG (antithyroglobulin) values throughout the course of disease. 10.4% of the patients had static TG levels. 64% of the patients with bone metastases showed 5-year survival.

Conclusion Multiple bone metastases represent a frequent complication of DTC especially of follicular thyroid cancer. In our population it is more common in females and in patients above 40 years of age. Overall survival rate is very good in the patients with bone metastasis if they are managed aggressively with total thyroidectomy and repeated radioactive iodine.

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Key words: Differentiated thyroid cancer, Bone metastases, Radioiodine treatment

Introduction

Carcinoma of thyroid is a potentially curable cancer. The estimated incidence of thyroid cancer has increased by 14.6% over the past 40 years, but the estimated death rate has fallen by 21%, probably as a result of earlier diagnosis [1]. Bone metastases from DTC occur in 2-13% of patients. After the age of 40 years, 10% of patients with papillary thyroid carcinoma (PTC), 25% of patients with follicular thyroid carcinoma (FTC), and 35% of patients with Hurthle cell carcinoma develop distant metastases [2]. When bone metastases are present, the overall survival at 10 years was reported to be up to 53% [1,3]. The extent of metastatic disease to the bone and its response to radioactive iodine are associated with survival. Palliative treatment is frequently the only option at diagnosis. Osteolytic lesions are invariable and they reduce the quality of life causing pain, fractures, and spinal cord compression [3].

The extent of metastatic disease to bone and its response to radioactive iodine are associated with survival. Palliative treatment is frequently the only option at diagnosis. Osteolytic lesions are invariable and they reduce the quality of life causing pain, fractures, and spinal cord compression [3]. Distant metastases from papillary carcinoma of the thyroid are uncommon and the subgroup of papillary carcinoma of the thyroid, which develops distant metastasis, is known to have a worse prognosis [3].

Differentiated thyroid cancer has a survival rate of 80-95%; however in DTC with distant metastases this rate comes down to 40%, and in cases with bone metastases, this further reduces to less than 21% [2, 4]. Bone metastases are from mainly follicular or less well-differentiated tumours and 80% occur within the axial skeleton. It leads to excessive bone resorption causing release of various growth factors, which stimulate further tumour growth. Remission rates for single lesions may be as high as 54%, but this falls to less than 3% with multiple bone metastases and usually occurs in those patients under 45 years of age with a small tumour burden and normal appearing skeletal x-rays [4].

The aim of this study was to investigate the prognostic factors of differentiated thyroid carcinoma patients with bone metastasis and to investigate the clinical efficacy of $^{131}$I therapy in these patients.

Patients & Methods

From January 2007 to June 2012, 360 patients with differentiated thyroid carcinomas were treated in our institute. Fifty-seven (15.8%) of the 360 patients had bone metastases. The medical records of these 57 patients were reviewed. We investigated the clinical characteristics of the patients including: the treatment received with respect to number of iodine-131 doses, the per patient dose, the importance of the 1st I-131 dose; the prognosis of patients with respect to their serial TG levels; symptomatic response in terms of pain, neurological deficits and reduction in local swelling, and their 5-year survival.

Results

The incidence of bone metastases in patients of differentiated thyroid carcinoma in our institute was found to be 15.8%. The mean age of the patients at the time of diagnosis of bone metastases was 47±18 years (range 16 to 80 years); 46% of these patients were below 40 yr of age and 53.8% patients were above 40 yr; 15.3% were males and 84.6% females.

The primary histological classification included papillary (38%) and follicular (45.6%) carcinoma. Multiple bone sites were involved in 50% patient; 29% of the patients had a solitary bone lesion; and 20.8% of the patients had metastases to other organs in addition to bone. All patients underwent thyroidectomy.
followed by multiple $^{131}$I therapy doses. Mean number of $^{131}$I doses received per patient ranged from 3-12 doses with a mean of 6.6 doses. Mean cumulative $^{131}$I dose given per patient ranged from 18130-76960 MBq with a mean dose of 48914 MBq.

Baseline thyroglobulin (TG) level was elevated in 93.8% patients and ranged from 380 ng/ml to 17300 ng/ml with a mean value of 2250 ng/ml ± 5644. Serial TG levels were done at 6-12 months intervals before each radioiodine therapy dose. 60% of patients showed a declining trend in TG over time, 23% of total patients showed rising trend, and 6.2% of the patients had normal TG/ATG (anti-thyroglobulin) values throughout the course of the disease. 10.4% of the patients had static TG levels.

Total drop in TG level was estimated in the course of treatment. 48-56% drop in TG level was noticed after 1st dose of $^{131}$I therapy (as a fraction of total drop in TG during treatment course).

The 5-year survival in patients with bone metastases was 64% (Figure 1). Clinical response in terms of reduction in pain, improvement in neurological deficits or reduction in local swelling was seen in 81% of the patients, whilst 19% of the patients showed no clinical response (Figure 2). None of the patients showed a deterioration with successive $^{131}$I treatments.

**Discussion**

Bone metastases from differentiated carcinoma thyroid can cause serious complications. Unfortunately, the occult clinical presentations usually delay the early diagnosis and proper management [1]. The incidence of bone metastases in differentiated carcinoma thyroid patients in our Institute was found to be 15.8%. This incidence, which is quite high when compared with previously reported incidences of 3.8%, 4.2% and 5.0% [1, 5, 6] may indicate a high prevalence of bone metastases in our local patient population. A study conducted in Tunisia showed similar prevalence as ours at 3.8-17.9% [7].

The mean age at the time of diagnosis of bone metastases was found to be 47±18 years (range 16 to 80 years). 46% of the patients were below 40 yr of age, whereas 53.8% of the patients were above 40 yr. It therefore appears that the presence or absence of bone metastases is not age-specific as due to the fact that it is equally prevalent in the older and the younger age groups in our population.
Carcinoma thyroid is more prevalent in females than males and this is also evident by the preponderance of females patients in our study with a higher percentage of female (84.6%) affected compared with males (15.3%).

A larger proportion of patients in our study with differentiated thyroid cancer and bone metastases, had follicular carcinoma (45.6%) compared with papillary carcinoma (38%). This is in concordance with the reported higher incidence of bone metastases in patients with follicular carcinoma (15.2-33.7%) compared with patients with papillary carcinoma (0.6-6.9%) [7].

A single bone site involvement was seen in 29% of the patients, multiple bone site involvement was seen in 50% of the patients, and 20.8% of the patients had metastases to other organs in addition to bone. Our results are in agreement with the results of previous studies [7, 1], which shows that multiple bone lesions occurred more frequently than single bone lesions. In patients with DTC with bone metastases, Kallel et al. reported multiple bone site involvement in 76% of patients [7] with Wu et al. in 56.8% [1].

All patients in our study underwent near total thyroidectomy followed by aggressive radiiodine therapy as evidenced by greater number (3-12 doses; mean 6.6) and higher $^{131}$I doses (mean dose per patient 48914± 20424 MBq. This may account for a lower proportion of our patients needing palliative surgery. Only 13% of our patients underwent palliative surgeries (e.g. decompression laminectomy, open reduction and internal fixations) compared with 38% (17/44 patients) reported by Kallel et al. [7].

Baseline thyroglobulin (TG) level ranged from 380ng/ml to 17300ng/ml with a mean value of 2250ng/ml ± 5644. In our study, 60% of patients showed biochemical response in terms of declining TG levels, while 23% of total patients showed a rising trend, 6.2% of the patients had normal TG/ATG (antithyroglobulin) values throughout the course of disease. 10.4% of the patients had static TG levels indicating static disease. Patients in our study population with higher TG levels at the time of diagnosis had poorer prognosis. Our results are in agreement with reported findings by Wang et al. who studied prognostic factors of DTC with pulmonary metastases [8].

Clinical response was seen in 81% patients with 19% of the patients showing a lack of clinical response. None of the patients showed deterioration with successive $^{131}$I treatments. Our results indicate that although bone metastasis are very resistant to therapy and difficult to cure, nonetheless $^{131}$I therapy has proved effective in treating bone metastasis from DTC. We noticed a 48-56% drop (as a fraction of total drop in TG during treatment course) in TG level after the first dose of $^{131}$I therapy. It appears that in cases of bone metastases the first dose given after thyroidectomy is very important and should be the maximum permissible dose to achieve maximum reduction in TG levels.

The 5-year survival in our study was 64%, which is in agreement with results of previous studies, with Schlumberger et al. and Ruegemer et al. reporting a calculated survival rate of 53%, which rose to 92% for <40-year age and dropped to 35% for >40-year age patients [9, 10]. In conclusion, the overall survival rate is very good in the patients with bone metastasis if they are managed aggressively with total thyroidectomy and repeated radioactive iodine.

References


Successful Ra-223 treatment with a long interval between the second and the third cycles: a case report

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Abstract

Ra-223 therapy is recommended for Castration Resistant Prostate Cancer (CRPC) patients with bone metastases. The standard protocol is 5-6 cycles of therapy with 4 weeks intervals to gain survival benefit.

We report a case of a chemo-naïve CRPC patient who after 1.5 years of androgen-deprivation therapy had widespread bone metastases, PSA of 4186 ng/ml, alkaline phosphatase (ALP) at 2982 U/l, bone marrow involvement with anaemia and thrombocytopenia. $^{223}$RaCl$_2$ therapy was started in August 2014. After the first two cycles of $^{223}$RaCl$_2$ PSA dropped to 70 ng/ml, ALP to 877 U/l. The third cycle was delayed for 5.5 months due to technical reasons. Unexpectedly, during Ra-223 therapy interruption the positive changes were still ongoing. PSA-level decreased further, to 0.28 ng/l and ALP to 254 U/l. Hb level increased from 101 to 125 g/l, PLT from 105 to 180x10$^9$/l. After the interruption the patient received 4 planned cycles. Control bone scan after the 4th cycle revealed pathological uptake only in shoulder joints and sternum. In the follow-up period the patient demonstrated minimal disease signs: with normal ALP level, PSA 0.11 ng/ml.

Ra-223 Therapy can give anti-tumour effect, as can be seen from the significant decrease in the PSA level. Breaks in Ra-223 Therapy are not dramatic. After interruption, it can be continued again. This fact can be taken into account while planning therapy. As shown here, clinical cases such the one we have reported, may allow a degree of flexibility to the standard recommendations on a case to case basis.

Key words: Radium-223, Castration resistant prostate cancer, Bone metastases

Introduction

Ra-223 chloride became a gold standard of treatment of Castration Resistant Prostate Cancer.
(CRPC) with bone metastases. ALSYMPCA trial and later investigations have shown benefit in overall survival in patients who received Ra-223 treatment compared with the placebo group [1, 2]. The standard protocol recommends 6 cycles of radium-223 therapy (55 kBq/kg dose) at 4-weekly intervals [3]. Survival benefit has been shown in patients who have completed all 6 cycles compared with those who received less than 5 cycles [4]. Sometimes, the following cycle can be delayed due to different reasons. The influence of these delays on the treatment outcome remains unclear. There are some retrospective data which have shown that there is no significant difference in the number of completed cycles or the median overall survival between those patients, who received their treatment in a planned way and those who experienced a 4-week treatment delay. Moreover, patients with unexpected treatment delay have shown significantly longer median progression free survival [5].

Circumstances may interfere with the treatment schedule, which may beg the question: what is better for the patient, switch to alternative treatment method or restart Ra-223 treatment? We present a clinical case of long-term treatment delay of 5.5 months between the 2nd and 3rd cycles where despite the delay the patient showed clinical benefit.

Case report

A 56-year-old man with high-grade prostate adenocarcinoma (Gleason 8) with widespread multiple bone metastases was diagnosed with CRPC after 1.5 years of initially successful androgen-deprivation therapy. After a relatively long period of stable disease under standard hormonal therapy, his PSA started to rise. The best standard-of-care at that time (February, 2014) was chemotherapy; however, the patient refused the treatment and opted for the then new investigational treatment with Ra-223. But as a result of a significant delay (6 months) in the starting date of the clinical trial, his PSA and ALP levels rose quite dramatically and he became mildly symptomatic for which he was prescribed analgesics. At the time of the start of treatment, his bone scan showed a “superscan” appearance, PSA was >4000 ng/ml and ALP level nearly reached 3000 (normal range: 0-120 U/l). Moreover, there was bone-marrow involvement, haemoglobin level dropped to 101 g/l, and platelet count dropped to 105 x10⁹/l. In August 2014, the patient received his first cycle of Ra-223, which was well tolerated, followed by the second cycle 4 weeks later. After the start of the treatment, the ALP level started to decline, and in 2 months time dropped from 2982 to 878 U/l (Figure 1); PSA level fell from 4186 to 70 ng/ml (Figure 2), Hb level and PLT counts remained on the border of acceptable (Figure 3 and 4).

Unfortunately, the patient couldn’t receive his third cycle of Ra-223 in time, due to unexpected supply disruption. After the first two cycles, there was clearly a good biochemical response but both tumour marker levels (PSA and ALP), remained much higher than normal. In this situation it was difficult to predict which was the better of the two options: 1) switch to chemotherapy (abiraterone and enzalutamide were not available) or 2) stay without any kind of treatment until supplies were restored. However, the patient himself refused to undergo chemotherapy again and decided to wait until the supply was restored, which period lasted for 5.5 months. Unexpectedly however, Ra-223 continued to have a beneficial effect. During the shortage period, the patient didn’t receive any kind of treatment except for continuing with his standard androgen deprivation therapy (Zoladex). Despite the fact that the patient was neither given chemotherapy nor any of the new hormone therapies, his PSA level continued to fall, and was measured at 0.28 ng/ml at the 5th month of supply interruption (Figure 2). ALP level also declined, but was still double the upper limit of the normal range (Figure 1). Thus, when the supplies restarted he received 4 additional cycles, so his
treatment which initially started in August 2014 completed late by June 2015.

The outcome of such unusual treatment schedule was nonetheless excellent with the bone scan, which was performed in April 2015 (after the 4th cycle of treatment), demonstrating nearly complete response, particularly when compared with the pre-treatment scan which had shown widespread skeletal involvement (Figure 5) and on the control bone scan only slight increase in 99mTc-MDP uptake in the shoulder joints and sternum could be seen (Figure 6).

This case also demonstrated a relatively long progression-free survival of 37 months duration. In September 2017, the PSA level again started to rise with the 11C-choline PET-CT revealing bone metastases only in the shoulder joints.
The Ra-223 treatment schedule was approved in randomized placebo-controlled trials. The ALSYMPCA trial demonstrated acceptable safety profile and positive influence on survival [1]. In fact, the treatment schedule was drawn empirically. Investigators stay on the idea, that the number of completed cycles can influence on survival independently from the PSA, ALP and radiologic dynamics [4]. The optimal time between consecutive cycles of Ra-223 remains unclear, different time schedules are not investigated. This clinical case demonstrated some unexpected advantages of long intervals between treatment cycles. When the patient started his Ra-223 therapy his blood counts were not very good, and he couldn’t be predicted to be able to complete all 6 cycles of the therapy. But during the treatment shortage his blood counts became normal. After resumption of the treatment, there was a slight decline in the platelet counts and haemoglobin level, which reflects the adverse effect of Ra-223. Thus, the unexpected shortage had some advantages in this clinical case.

A previous report suggests that longer intervals between therapy cycles can prolong progression-free survival [5]. This clinical case has demonstrated possible advantages of long treatment intervals for patients with widespread bone disease and bone marrow involvement and a high risk of haematologic adverse events. In all reported cases the treatment delays were unplanned, but outcomes of these cases were positive. Thus, it appears that in some cases, the treating physician may consider changing Ra-223 treatment schedule in order to allow bone marrow to recover and prevent possible haematotoxicity.

On the merit of this individual case, it may be assumed that in patients who show a good response to Ra-223, the occasional unavailability of Ra-223 for the following cycle, there may not be a need to switch to other kinds of therapy. It is however important to change treatment strategy in cases where there is evidence of disease progression.

**Figure 5** Pre-treatment whole-body bone scan with $^{99m}$Tc-MDP on 7 Aug 2014 in the anterior (left) and posterior (right) projections showing “superscan” appearance

**Figure 6** Post-treatment whole-body bone scan with $^{99m}$Tc-MDP after the 4th treatment cycle on 21 Apr 2015 in the anterior (left) and posterior (right) projections showing almost complete resolution
Conclusion

This case report has demonstrated that Ra-223 acts much longer than 28 days, and has underscored the fact that treatment delays may not have a significant influence on overall patient survival. Moreover, in some clinical cases it may be better to lengthen the interval between consecutive therapy cycles, particularly in patients with widespread bone metastases and a low bone marrow reserve.

Acknowledgement

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References


CASE REPORT

Cutaneous flow pattern of primary lymphoedema

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Abstract
A case of a patient with primary lymphoedema where the scan pattern could have easily been confused with that of secondary lymphoedema is presented. This image pattern though occasionally seen has not previously been reported.

Key words: Lymphoscintigraphy, $^{99m}$Tc-Nanocolloid, Primary lymphoedema

Introduction
Qualitative lymphoscintigraphic image evaluation and interpretation yields specific image patterns associated with primary lymphoedema (e.g. aplasia or hypoplasia) or secondary lymphoedema (e.g. post surgical or post traumatic). An awareness of these patterns is crucial to making correct scan interpretation and accurate diagnosis. We present a case of a patient with primary lymphoedema where the scan pattern could have easily been confused with that of secondary lymphoedema. This image pattern though occasionally seen has not previously been reported.

Case report
A 26-year-old female with left lower limb oedema of 16-month duration was referred to the nuclear medicine department at the Farwania Hospital Kuwait, for lymphoscintigraphy to determine the underlying cause of her lower limb swelling.

Dynamic lymphoscintigraphy was performed for 45 min following bipedal injections of $^{99m}$Tc-Nanocolloid into the first interdigital web spaces of the feet. Next, pre- and post-exercise static lower half-body scans were acquired. The early flow images did not show inguinal lymph nodes on either side, nor any activity in the lymphatic channels (Figure 1). The delayed post-exercise images showed appearances suggestive of dermal backflow in the left mid thigh (Figure 2). On the right, there was no activity seen above the mid calf level with apparent patchy dermal back flow only to this level. On careful review of the images, the pattern of the pooling of activity in the skin was seen to be significantly different than the classic dermal backflow pattern (Figure 3) and the appearances were in keeping with cutaneous lymphatic microcirculatory flow through the lymphatic to flow through dilated...
dermal lymphatic channels in secondary lymphatic obstruction (Figure 3). A diagnosis of bilateral congenital lymphoedema secondary to lymphatic aplasia/hypoplasia was established.

Discussion

Normal extremity lymphatic drainage occurs through: 1) the superficial (epifascial) lymphatics that drain the skin and the subcutaneous tissue and 2) deeper lymphatics which drain subfacial structures [1]. Radiocolloid particles following subcutaneous injection will be transported through the superficial lymphatics into the lymphatic channels. In secondary lymphoedema due to obstruction of the lymphatic channels, there is “backflow” of lymph at and below the

Figure 1  Early flow images showing absent flow in the deep lymphatic channels with non-visualisation of the inguinal lymph nodes

Figure 2  Delayed post-exercise images showing appearances suggestive of dermal backflow on the left side extending up to the mid thigh level

Figure 3  Classic dermal backflow pattern in a patient with secondary lymphoedema (A) with the image on the right showing a normal lymphoscintigram for comparison (B)
level of the obstruction, from the lymphatic channels into the dermal lymphatics, giving rise the pathognomic “dermal backflow” sign, which is typically seen as increased uptake in the skin with dilated dermal lymphatics and an abrupt or “spirit level” type cut-off (Figure 3 shows the typical “dermal backflow” in a patient with secondary lymphoedema). However, in primary lymphoedema, where there is aplasia or hypoplasia of the primary lymphatic channels, the lymphatic flow is reversed with predominant preferential flow through the dilated cutaneous epifascial lymphatics. This cutaneous lymphatic flow is characterised by diffuse increased superficial uptake ascending upwards toward the thigh without any cut-off as can be seen in Figure 2. In the absence of obstruction the normal physiological flow through the superficial and the deeper lymphatic networks remain separate; however, there is preferential flow through one or the other lymphatic network depending on the nature of the obstruction (primary vs. secondary).

**Conclusion**

Dermal backflow is a feature of secondary lymphoedema and is absent in primary lymphoedema. This new image pattern of “cutaneous flow” on delayed imaging in primary lymphoedema that mimics the “dermal backflow” pattern in secondary lymphoedema has to date not been reported.

An awareness of this “cutaneous” flow pattern is important for correctly diagnosing primary and secondary lymphoedema cases through qualitative image evaluation and interpretation of lymphoscintigrams.

**References**

Bone scintigraphy in apatite-associated destructive arthritis (Milwaukee shoulder syndrome)

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Abstract

We report a case established of Milwaukee shoulder syndrome (apatite-associated destructive arthritis) and describe the bone scintigraphic, radiologic and histologic findings, which are compared with a similar case of rapid non-crystal-deposition arthritis. The cases shall add to the differential diagnosis of shoulder arthropathy on bone scintigraphy.

Key words: Milwaukee shoulder syndrome, Bone scan, Arthritis,

Introduction

Milwaukee shoulder syndrome is a destructive arthropathy associated with calcium hydroxyapatite and calcium pyrophosphate dehydrate crystal deposition mostly affecting elderly females. We describe the bone scintigraphic pattern observed in a patient with an established diagnosis of Milwaukee shoulder syndrome and in another patient in whom the diagnosis was suspected on the basis of the bone scan appearances. The aim of the report is to introduce this syndrome and document the bone scintigraphic findings for the differential diagnosis of shoulder arthropathy. A basic knowledge of this condition is important in order to recognize the uptake pattern often seen in patients undergoing bone scans with the primary complaint of painful shoulder joints.

Case 1

A 76-year-old lady with chronic renal failure presented with bilateral shoulder pain and swelling without any preceding history of trauma. Her x-rays of the shoulders showed joint narrowing, subchondral sclerosis and subchondral bone destruction, and calcifications in the joint capsule. There was bilateral rotator-cuff tear. US of the shoulders showed fluid collection and synovial thickening. Synovial fluid was aspirated which appeared haemorrhagic and positive for calcium apatite crystals. The patient was referred to the nuclear medicine department for a bone scan in Nov 1997.

Multiple spot views of the skeletal were obtained to cover the entire skeleton 3 hours after an intravenous injection of 600 MBq...
Figure 1  Bone scan spot views of the skeleton in patient 1. Not the intense increased bilateral shoulder joint uptake and the increased uptake in the lateral compartment of the right knee with degenerative changes in the spine, the hands and wrists and the left foot.
99mTc-methylene diposphonate using a single-head camera fitted with a low-energy high-resolution collimator. The bone scan images (Figure 1) showed a high bone/soft-tissue ratio with poor visualization of the kidneys consistent with the known chronic renal failure. There was intense increased uptake in both shoulder joints as well as the lateral compartment of the right knee. These changes taken together with the x-rays and the synovial fluid microscopy were consistent with Milwaukee shoulder syndrome. There was also increased uptake seen in both 1st carpo-metacarpal joints and in the left tarsal region and the base of the 1st left toe consistent with arthritis. The changes in the shoulders were thought to be typical of Milwaukee shoulder syndrome and on basis of the increased uptake in the lateral compartment of the right knee, the knee joint was also thought to be involved but wasn’t further investigated. The other joins with active arthropathy were thought to be possibly involved. The patient was treated with colchicine and physiotherapy with symptomatic relief.

Case 2

A 97-year-old lady who presented with bilateral chronic shoulder and right hip pain
referred to the nuclear medicine department of the Royal Hospital Haslar in Gosport, UK in Sep 2000. X-rays of the shoulders showed joint space narrowing with degenerative changes and joint and peri-articular soft-tissue calcifications.

A whole-body bone scan was performed 3 hours after an intravenous injection of 640 MBq $^{99m}$Tc-methylene diposphonate using a double headed ADAC gamma camera fitted with a low-energy high-resolution collimator. The whole-body bone scan images (Figure 2) showed crescent-shaped areas of intense increased uptake in both shoulders corresponding to the glenohumeral joints. A similar pattern of intense increased uptake was seen in the right hip. There changes were consistent with active destructive arthritis of the bilateral shoulder and the right hip joints. The bone scan also showed scoliosis of the lumbar spine and focal increased uptake in the right 10-12 ribs posteriorly consistent with rib fractures. X-rays of the shoulders showed moderate degenerative changes. The scintigraphic features were very suspicious of Milwaukee shoulder syndrome and the patient was further investigated to establish or exclude the diagnosis. The bilateral large effusions in the shoulder joints were aspirated. The aspirated fluid showed some lymphocytes and macrophages but no crystals were identified. Rheumatoid factor was negative and there was positive ANA with homogenous pattern which was thought to be of doubtful significance. The case was thought to be due to non-specific advanced active arthropathy as a result of failed microscopic diagnosis of Milwaukee shoulder syndrome.

Discussion

Milwaukee shoulder syndrome (MSS) was first reported in 1981 in 4 elderly female patients from the state of Milwaukee in the United States. The term was coined to describe the radiological, clinical and histological features seen in the shoulder joints of these patients with chronic recurrent severe shoulder joint arthritis and joint effusions with x-rays showing rotator cuff tears and severe degenerative joint disease [1-3]. Another report a year later described similar features introducing the term of rapid destructive arthritis of the shoulders for the disease [4]. Further studies introduced other terms for the disease including haemorrhagic shoulder of the elderly, rapid destructive arthritis of the shoulder, apatite-associated destructive arthritis and idiopathic destructive arthritis of the shoulder, crystal deposition disease, crystal-induced arthritis, etc. [5].

The involved joints show massive effusion, which is characteristically non-inflammatory, haemorrhagic with intraarticular calcium hydroxyapatite deposition that causes release of lysosomal enzymes resulting in destruction of the peri-articular tissue specially the rotator cuff as well as the articular cartilage. The shoulders are the most frequently involved joints but other joints such as the elbows, wrists, hands, hips, knees, and the feet as well as the cervical and lumbar spine can be affected [6]. Elderly age-group patients are mostly affected with a male:female ratio of 1:4 [6-8].

The bone scan shows intense uptake in the affected joints as well in the peri-articular calcific soft-tissue deposits. Both of our cases showed a similar pattern of uptake on the bone scan in the shoulders though the right knee was seen to be involved in Case 1 where the uptake was seen to involve lateral tibiofemoral compartment, which is the reported pattern of knee involvement in Milwaukee shoulder-knee syndrome [9]. A somewhat characteristic appearance of crescentic increased activity in the joint cavity as compared with that seen in the articular regions was observed, presumably due to bone crystal uptake in these cases of crystalline arthropathy (Figures 1 & 2). Although bone scintigraphy in these patients is highly sensitive, it appears rather non-specific with the scintigraphic features similar to those seen in other types of arthritis.

The bone scan of the patient in Case 2 showed intense bilateral glenohumeral joint and right hip joint uptake with peak of activity confined to the joint cavity (Figure 2). This uptake pattern was similar to that seen in Case 1, but
here microscopy revealed absence of crystals. Despite this, the case was clinically diagnosed and treated as Milwaukee shoulder syndrome. The detection of basic calcium phosphate (BCP) crystals in the synovial fluid of patients with arthropathy is challenging due to the submicroscopic size of BCP, the complex nature of the matrix in which they are found and the fact that other crystals can co-exist with them in cases of mixed pathology [10]. Routine analysis of joint crystals relies almost exclusively on the use of optical microscopy, which has limited applicability for BCP crystal identification due to limited resolution and the inherent subjectivity of the technique [10].

The key mechanisms whereby BCP crystals may cause tissue damage are: (1) the induction of mitogenesis; (2) the upregulation of matrix metalloproteinase (MMP) production; (3) the stimulation of cyclooxygenases 1 and 2 and prostaglandin E2 production; (4) the stimulation of cytokine production, and (5) the induction of nitric oxide production [11].

Factors that may predispose to this syndrome include deposition of calcium pyrophosphate dihydrate crystals, direct trauma or chronic joint overuse, denervation and chronic renal failure [12]. Chronic renal impairment was the predisposing risk factor in Case 1 in this report.

The treatment in these cases is supportive and involves resting the affected joint(s), prescription of nonsteroidal anti-inflammatory agents. Refractory cases are suitably treated with substitution of magnesium-containing NSAID and oral chochicine [13].

References


A striking case of florid multifacial soft-tissue infection on an FDG-PET scan

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**Key words**: PET/CT scan, 18F-FDG, infection, soft-tissue.

**Background** A 24-year-old male had a road traffic accident in which he sustained a crush injury to his right lower leg and a compound fracture of the right femur, which were respectively treated with below knee amputation and metallic nailing of the right femur. The patient presented to the outpatient clinic 7 years later with 1-month history of pain and swelling of the right thigh; however, he didn't report any fever. An FDG-PET scan was prescribed to rule out infection.

**Procedure** 18F-fluorodeoxyglucose (329 MBq) was injected intravenously and PET/CT imaging performed after 60 minutes on a PET/CT camera (GE 710). A CT scan without oral or intravenous contrast, without breath holding, was acquired at low mA level for attenuation correction and localization purposes only. Arms were held up. Subsequently PET images from vertex to toe were obtained. PET, CT and fused images were reconstructed in the transaxial, coronal and sagittal axes (Figure 1).

**Findings** The PET/CT scan images show extensive accumulation of FDG-avid fluid in the right thigh starting from the level above the nail in the mid gluteal region. Focal uptake is seen in the soft-tissue above the femoral neck with the high FDG uptake (SUV\text{max} 12.7). There is FDG-avid fluid surrounding the intramedullary nail (SUV\text{max} 3.8 to 5.9). The PET/CT scan shows extensive hypermetabolic fluid uptake in the right thigh in different soft-tissue regions including: 1) subcutaneously in the lateral aspect of the right thigh, 2) from mid to lower right thigh (SUV\text{max} 12.6), 3) intra-facial, 4) sub-facial, 5) intraseptal, 6) inter and intramuscular (SUV\text{max} 9 to 15.5). See Figures 1-3.

**Conclusion** The PET/CT scan findings were consistent with multiple hypermetabolic abscesses at different soft-tissue levels in the right thigh. There was however no evidence of osteomyelitis seen.

**Comments** Hybrid positron emission tomographycomputed tomography (PET/CT) with the glucose analogue, 18F-fluoro-2-deoxyglucose (18F-FDG), is being increasingly used for the diagnosis of musculoskeletal infection. Activated granulocytes present at sites of infection/inflammation use glucose as an energy source and avidly take up FDG, which is transported into the cells and phosphorylated by hexokinase to 18F-fluoro2-deoxyglucose-6-phosphate, that is not further metabolized. Increased cellular metabolism in the activated...
Figure 1  PET-CT scan showing MIP PET image in the left column and transaxial fused PET/CT images at corresponding levels (arrows) in the right column.

Figure 2  PET-CT scan sagittal images from left to right showing: CT scan image, PET image, fused PET/CT image and the MIP PET image. Note the uptake in the fascial planes of the different muscle compartments.
inflammatory cells results in an increased expression of glucose transporter (GLUT) proteins by these cells, which coupled with an increase in the affinity for glucose by the glucose transporters secondary to the effects of cytokines and growth factors, results in high FDG uptake at sites of infection/inflammation [1, 2].

This striking case of florid and extensive soft-tissue infection in the right thigh 7 years post surgery demonstrates the effectiveness of this new infection imaging modality in the non-invasive diagnosis of infection. The combination of PET and CT provides complementary information at a higher resolution and sensitivity as compared with single-photon emitting radionuclides.

**Figure 3** Coronal PET-CT scan images with CT scan image (left), PET image (middle) and fused PET/CT image (right). Note the uptake in the fascial planes of the different muscle compartments without any increased bone uptake seen to suggest the presence of osteomyelitis.
FDG-PET technique demonstrates the metabolic changes that occur earlier compared to the anatomical changes seen by CT or MRI alone. The high metabolic activity of infective abscesses due to a high degree of FDG avidity coupled with structural CT changes of infection facilitates rapid interpretation of both the severity and the extent of infection and helps delineate osseous from soft-tissue involvement. The PET/CT scan in this case showed multiple hypermetabolic areas which were precisely localized to the soft-tissue and showed no bone involvement. The findings are extremely helpful in determining and instituting the appropriate treatment and also useful for monitoring the therapeutic efficacy.

References


Unusual breast radioiodine uptake in a non-breastfeeding woman with papillary thyroid carcinoma

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Key words: Whole-body scintigraphy, radioiodine, papillary thyroid carcinoma, soft-tissue uptake

Background A 48-year-old woman underwent total thyroidectomy for a multinodular goiter. Histopathological examination revealed papillary thyroid carcinoma.

The patient was referred to the nuclear medicine department for ablative dose of iodine-131 iodine (3.7 GBq) and post therapy radioiodine scan. Thyroglobulin level was at 11 ng/ml.

Procedure Planar whole-body radioiodine scintigraphy was performed in the anterior and posterior projections 5 days after the ablative dose of $^{131}$I. Single-photon emission computed tomography (SPECT-CT) was additionally performed for anatomical localization of the thoracic radioiodine-avid foci.

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Figure 1 Planar $^{131}$I whole-body scan showing two thoracic radioiodine-avid foci probably outside the pulmonary fields
Findings The whole-body radioiodine scan revealed cervical radioiodine uptake, in relation to a post-surgical residue.

The scan also showed two quasi-symmetrical thoracic radioiodine-avid foci located probably outside the pulmonary fields (Figure 1). On the SPECT-CT scan these thoracic foci of radioiodine uptake were seen to correspond to uptake in both breasts (Figure 2).

Conclusion Whole-body scintigraphy after $^{131}$I ablation showed unusual bilateral focal uptake in the breasts in a patient with papillary thyroid carcinoma. This appears to be a rare case of false-positive uptake in a non lactating woman.

Comments The knowledge of the usual sites of radioiodine concentration in the body is essential for the correct interpretation of the whole-body scintigraphy. However, the real pitfall in the correct diagnosis is concentration of $^{131}$I in a lesser known site.

Physiological uptake of radioiodine can be observed in a variety of non-thyroidal tissues, breast is one of them, because of its expression of NIS; iodine accumulation in the lactating breast has been recognized for the last 64 years and is now regarded as a usual finding in postpartum patients [1]. However, concentration of radioiodine in non-lactating breasts is rare with the first such case reported by Sitterson in 1962 [2].

Hammami et al. studied the significance of radioiodine uptake by the non-lactating breast [3]. Expressible galactorrhoea and moderately elevated prolactin levels were observed in 48% and 24% of cases, respectively. Other rare causes of breast radioiodine uptake have been described, which include breast fibroadenoma [4] and breast carcinoma [5].

References


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