
ESTIMATION ON CLINICAL JUSTIFICATION FOR THE ESTABLISHMENT OF COPPER-64 RADIOISOTOPE PRODUCTION AND COPPER-64 RADIOPHARMACEUTICALS APPLICATION

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Abstract: Establishing the production of radiopharmaceuticals and introducing new radiopharmaceuticals into healthcare practice in a developing country is challenging, primarily from an economic point of view. A feasibility study provides an objective assessment that takes into account not only the economic aspect but also the clinical impact and development of research potential. The first phase of the feasibility study for the establishment of copper-64 radioisotope production is a preliminary analysis, which aims to assess whether the introduction of ^{64}Cu -radiopharmaceuticals into clinical use is possible and justified. The preliminary analysis includes a review of statistical data on malignant diseases on a national level based on reference databases, international and domestic, and a review of data on the clinical application of ^{64}Cu -radiopharmaceuticals based on a reference database for clinical trials. As to the cancer statistics review, for a more objective insight into assessing the justification for introducing new radiopharmaceuticals into clinical use, data on malignancies in North Macedonia were compared with data related to the world, southern Europe and the European Union. The comparison focused on data relating to lung, cervical, and brain neoplasms as cancers examined in clinical trials involving [^{64}Cu][Cu(ATSM)] radiopharmaceutical, one of the most widely explored ^{64}Cu -radiopharmaceuticals. As can be seen from the comparison, cervical cancer has a lower incidence and mortality in Macedonia than in the world but a higher incidence and mortality compared to southern Europe and the countries of the European Union. Lung and brain cancers have a higher incidence and mortality in Macedonia than in all other compared regions. The results of the cancer statistic review indicate that it is rational to adopt strategies which can contribute to better management of malignant diseases in Macedonia. One of those potential strategies could be introducing new radiopharmaceuticals in nuclear medicine practice. As for solid malignant tumors, the detection of tumor hypoxia is of particular importance to optimize the treatment strategy and improve the overall prognosis. Positron emission tomography with hypoxia-avid radiopharmaceutical is a noninvasive method for measuring hypoxia, highly sensitive and directly quantitative. Considering the results of the preliminary analysis, it is reasonable to proceed to the next stages of the feasibility study for the establishment of the production of ^{64}Cu radioisotope and the implementation of ^{64}Cu -radiopharmaceuticals in clinical practice in Macedonia. Radiopharmaceuticals based on copper-64 radioisotope are promising due to the unique properties of this radionuclide that are complementary for diagnostic and/or therapeutic purposes.

Keywords: copper-64, cancer incidence, cancer mortality, positron emission tomography, radiopharmaceuticals

1. INTRODUCTION

Copper-64 (^{64}Cu) is a promising radionuclide with unique physical properties (half-life and decay scheme) making it suitable for positron emission tomography (PET) imaging and radionuclide therapy. Given the half-life of 12.7 h and the well-established coordination chemistry, ^{64}Cu is adequate for linking with both, molecules which manifest rapid pharmacokinetics, such as small molecules and peptides, as well as slow pharmacokinetic agents, such as monoclonal antibodies and stem cells (Jalilian and Osso, 2017; IAEA, 2022). One of the most widely explored ^{64}Cu -based radiopharmaceuticals is [^{64}Cu][Cu-diacetyl-bis(N(4)-methylthiosemicarbazone)] ([^{64}Cu][Cu(ATSM)]), which has shown promise in clinical trials (non-small-cell lung cancer, cervical cancer, head and neck cancer, glioblastoma) as a hypoxia selective tracer and as an indicator of response to treatment and tumour recurrence (IAEA, 2022; Liu et al., 2020; Lopci et al., 2016; Xie, F., & Wei, W., 2022; Zhou et al., 2019). Recently,

[⁶⁴Cu][Cu(ATSM)] was also used for oxidative stress imaging in early Alzheimer's disease and for renal blood flow measurement using PET/MRI modalities (Nishikawa et al., 2023; Okazawa et al., 2023). Hypoxia is a common and important feature of solid malignancies and is typically associated with malignant progression, metastasis, resistance to chemo- and/or radiotherapy, recurrence, and overall poor prognosis. One of the non-invasive techniques for detecting tumor hypoxia is positron emission tomography, which is a three-dimensional, direct assessment of intratumoral oxygen levels (Li et al., 2021; Liu et al., 2020). Several radiopharmaceuticals are used for PET imaging of hypoxia. The advantages of [⁶⁴Cu][Cu(ATSM)] over other PET radiopharmaceuticals used for hypoxia detection are simple and rapid radiolabelling, faster clearance from normoxic tissues (allowing a short time between injection and imaging), a simple method for quantification, and very good image quality (Bourgeois et al., 2011; Gutfilet et al., 2018).

As part of the feasibility study for the establishment of copper-64 production in North Macedonia, in order to assess whether the clinical application of ⁶⁴Cu-radiopharmaceuticals in the country is possible and justified, a preliminary analysis has been conducted. The preliminary analysis comprises a review of statistical data regarding malignant diseases in Macedonia and a review of clinical applications data of ⁶⁴Cu-radiopharmaceuticals. This article aims to present the methodology and results of the preliminary analysis regarding the review of cancer statistics (incidence and mortality).

2. MATERIALS AND METHODS

The review of statistical data regarding malignant diseases (incidence and mortality) was based on a literature search on the reference databases: national (Cancer Register and Mortality Register of Institute of Public Health) and international (Global Cancer Observatory). The review of cancer statistics focused on data related to the statistics of malignant diseases at the national level, but a comparison was also made. Data regarding the cancer statistics in North Macedonia were compared with the data on malignant diseases at the world level, in the European Union and southern Europe.

The European Union (EU-27 as indicated in the tables) includes the population of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the Netherlands. Southern Europe includes the population of Albania, Andorra, Bosnia and Herzegovina, Croatia, Cyprus, Gibraltar, Greece, Holy See, Italy, Malta, Montenegro, North Macedonia, Portugal, San Marino, Serbia, Slovenia, and Spain.

Given that [⁶⁴Cu][Cu(ATSM)] is one of the most commonly used ⁶⁴Cu-radiopharmaceuticals in clinical studies, a comparison was also made of the data relating to the cancers examined in the clinical trials involving this radiopharmaceutical. The comparison included data on lung, cervical and brain cancers. A comparison was not made for head and neck cancer because there are many types of cancer that affect the head and neck, collectively known as head and neck cancer.

3. RESULTS

As the Mortality Register demonstrates, after diseases of the circulatory system, cancer is the second leading cause of death in Macedonia. In 2020, 12.68% of deaths in the population older than 64 years and 24.25% of deaths in the population from 1 to 64 years of age were due to neoplasms.

As shown in Cancer Register, from 2011 to 2020, the average mortality rate from cancer in both sexes was 180 per 100,000 population (in women, 146 per 100,000 population and in men, 215 per 100,000 population). For the same ten-year period, lung cancer was the leading cause of cancer mortality in the male population in Macedonia (average mortality rate 63.9 per 100,000 men) and breast cancer in the female population (average mortality rate 29.07 per 100,000 women).

On average, there were 6,808 new cases per year, or 328 cases per 100,000 inhabitants, for the period from 2011 to 2020. About 87.8% of cancer cases were among the population over 50 years of age, of which 19.3% were between 50 and 60 years of age. The leading cause of cancer incidence in Macedonia from 2011 to 2020 was lung cancer (13.12% of all reported cases). The most frequent cancer in men was lung cancer (18.80% of the total reported cases), and the most common cancer in women was breast cancer (25.29% of the total reported cases). The most common cancer diagnoses in Macedonia, for the period from 2011 to 2020, are shown in Table No.1.

Table No.1 10 most common primary cancer sites, North Macedonia, 2011 - 2020

Total			Females			Males		
Code	Primary sites	%	Code	Primary sites	%	Code	Primary sites	%
C34	Bronchus and lung	13.12	C50	Breast	25.29	C34	Bronchus and lung	18.8
C50	Breast	11.59	C44	Other of skin	7.38	C61	Prostate	9.77
C44	Other of skin	8.22	C54	Corpus uteri	7.30	C44	Other of skin	8.90
C18	Colon	6.1	C34	Bronchus and lung	6.16	C16	Stomach	7.50
C16	Stomach	6.06	C18	Colon	5.61	C18	Colon	6.50
C61	Prostate	5.38	C53	Cervix uteri	5.16	C67	Bladder	5.67
C22	Liver and intrahepatic bile ducts	4.2	C16	Stomach	4.30	C22	Liver and intrahepatic bile ducts	5.08
C20	Rectum	4	C56	Ovary	3.83	C20	Rectum	4.38
C67	Bladder	3.93	C20	Rectum	3.53	C32	Larynx	3.85
C54	Corpus uteri	3.28	C22	Liver and intrahepatic bile ducts	3.11	C25	Pancreas	3.10

Among 7,632 new cases of cancer in 2020 in Macedonia, as indicated in the Global Cancer Observatory database, the five most frequent malignant diseases in both sexes, excluding non-melanoma skin cancer, were neoplasms of the lung (14.9 %), breast (12.9 %), colorectum (12.4 %), prostate (10.3 %), corpus uteri (4.8 %). The ten most common cancer diagnoses among new cases in 2020 in North Macedonia, compared to new cancer cases worldwide, in the EU-27 and Southern Europe are given in Table No.2.

Table No.2 New cancer cases in 2020, excluding non-melanoma skin cancer, both sexes

World		EU-27		Southern Europe		North Macedonia	
Cancer	%	Cancer	%	Cancer	%	Cancer	%
Breast	11.7	Breast	12.1	Breast	12.6	Lung	14.9
Lung	11.4	Prostate	11.4	Lung	11	Breast	12.9
Prostate	7.3	Lung	10.8	Prostate	10.3	Prostate	10.3
Colon	6	Colon	7.4	Colon	8.6	Rectum	6.7
Stomach	5.6	Bladder	5.3	Bladder	6.5	Colon	5.6
Liver	4.7	Rectum	3.9	Rectum	4.1	Corpus uteri	4.8
Rectum	3.8	Melanoma of skin	3.6	Pancreas	3.2	Bladder	4.8
Cervix uteri	3.1	Pancreas	3.2	Stomach	3.2	Stomach	4.3
Oesophagus	3.1	Kidney	2.9	Non-Hodgkin lymphoma	3	Brain, central nervous system	4
Thyroid	3	Non-Hodgkin lymphoma	2.9	Kidney	2.9	Pancreas	3.6

In women, among the new cases in 2020 in Macedonia, the most frequent were malignant neoplasms of the breast (29.2 %), colorectum (14.4 %), corpus uteri (10.9 %), lung (7.2 %), cervix uteri (3.3 %). Table No.3 shows the five most common cancers among new cases in women in 2020 in the four compared regions.

Table No.3 Top 5 most frequent cancers among new cases in females in 2020, excl. non-melanoma skin cancer

World		EU-27		Southern Europe		North Macedonia	
Cancer	%	Cancer	%	Cancer	%	Cancer	%
Breast	24.5	Breast	26.4	Breast	28	Breast	29.2
Colorectum	9.4	Colorectum	11.2	Colorectum	12.2	Colorectum	14.4
Lung	8.4	Lung	8.4	Lung	7.1	Corpus uteri	10.9
Cervix uteri	6.5	Corpus uteri	5.4	Corpus uteri	5.6	Lung	7.2
Thyroid	4.9	Melanoma of skin	3.8	Thyroid	3.9	Cervix uteri	3.3

In men, among the new cases in 2020 in Macedonia, the most frequent were malignant neoplasms of the lung (21 %), prostate (18.5 %), colorectum (10.9 %), bladder (7.0 %), and stomach (5.2 %). Table No.4 shows the five most

common cancers among new cases in men in 2020 at the world level, in EU-27, Southern Europe and North Macedonia.

Table No.4 Top 5 most frequent cancers among new cases in males in 2020, excl. non-melanoma skin cancer

World		EU-27		Southern Europe		North Macedonia	
Cancer	%	Cancer	%	Cancer	%	Cancer	%
Lung	14.3	Prostate	20.9	Prostate	18.8	Lung	21
Prostate	14.1	Lung	12.8	Lung	14.1	Prostate	18.5
Colorectum	10.6	Colorectum	11.9	Colorectum	13.6	Colorectum	10.9
Stomach	7.1	Bladder	7.6	Bladder	9.3	Bladder	7
Liver	6.3	Melanoma of skin	3.5	Stomach	3.6	Stomach	5.2

Table No.5 demonstrates the first ten malignancies concerning the mortality from malignant diseases in 2020 in the four compared regions. In Macedonia, regarding the deaths caused by cancer in 2020, the first ten malignant diseases were the neoplasms of the lung (23.3 %), breast (7.5 %), prostate (7.1 %), stomach (6.6 %), pancreas (6.4 %), colon (6.0 %), brain, central nervous system (6.0 %), rectum (5.8 %), liver (4.4 %), and bladder (3.1 %).

Table No.5 Mortality (deaths of cancer in 2020), both sexes

World		EU-27		Southern Europe		North Macedonia	
Cancer	%	Cancer	%	Cancer	%	Cancer	%
Lung	18	Lung	20.3	Lung	20.2	Lung	23.3
Liver	8.3	Colon	8.5	Colon	9.5	Breast	7.5
Stomach	7.7	Breast	7.2	Breast	6.8	Prostate	7.1
Breast	6.9	Pancreas	7	Pancreas	6.7	Stomach	6.6
Colon	5.8	Prostate	5.5	Stomach	5.1	Pancreas	6.4
Oesophagus	5.5	Liver	4.2	Liver	5	Colon	6
Pancreas	4.7	Stomach	4.1	Prostate	4.8	Brain, central nervous system	6
Prostate	3.8	Bladder	3.9	Bladder	4.2	Rectum	5.8
Cervix uteri	3.4	Rectum	3.6	Rectum	3.4	Liver	4.4
Rectum	3.4	Leukaemia	3.4	Leukaemia	3.4	Bladder	3.1

Table No.6, Table No.7 and Table No.8 show the comparison of the data (incidence and mortality) on cancers of the lung (C33-C34), cervix (C53) and brain, central nervous system (C70-C72), respectively.

Table No.6 Lung cancer (C33-C34), new cases and mortality, in 2020

Lung cancer	World	EU-27	Southern Europe	North Macedonia
New cases (%)	11.4	10.8	11.0	14.9
Mortality (%)	18.0	20.3	20.2	23.3

Table No.7 Cervical cancer (C53), new cases and mortality, in 2020

Cervical cancer	World	EU-27	Southern Europe	North Macedonia
New cases (%)	3.1	1.0	0.95	1.5
Mortality (%)	3.4	1.1	0.88	1.5

Table No.8 Brain, CNS cancer (C70-C72), new cases and mortality, in 2020

Brain, CNS cancer	World	EU-27	Southern Europe	North Macedonia
New cases (%)	1.6	1.5	1.6	4.0
Mortality (%)	2.5	2.7	2.9	6.0

4. DISCUSSIONS

A feasibility study for the establishment of copper-64 radioisotope production and the implementation of ⁶⁴Cu-radiopharmaceuticals in clinical practice in North Macedonia is being conducted at the University Institute for Positron Emission Tomography (UI PET), the only centre for the production of PET radioisotopes and radiopharmaceuticals in the country. As the first phase of the feasibility study, a preliminary analysis has been performed. Aiming to estimate whether there is a field for the application of ⁶⁴Cu-radiopharmaceutical preparations

in our country, the preliminary analysis includes a review of statistical data on malignant diseases (incidence and mortality) and a review of clinical applications data of ^{64}Cu -radiopharmaceuticals. Regarding the cancer statistics review, a comparison was made for a more objective insight into assessing the justification for introducing new radiopharmaceuticals into clinical use: data on malignancies in Macedonia were compared with data related to the world, southern Europe and the European Union. Malignant diseases are an important cause of morbidity and mortality worldwide, in every world region, irrespective of the level of human development, but cancer distribution doesn't follow the same pattern globally, among other things, due to socioeconomic conditions (Sung et al., 2021). Southern Europe, since it includes Macedonia, and the European Union, since it includes most of the high-income countries in Europe (according to the World Bank classification Macedonia is in the group of upper middle income countries), were chosen as regions for comparison. The comparison focused on lung, cervical and brain cancers, the solid malignancies that were targeted in clinical studies with $^{64}\text{Cu}[\text{Cu}(\text{ATSM})]$, one of the most widely explored ^{64}Cu -radiopharmaceuticals.

As for lung cancer, in the last decade, it was the most diagnosed cancer in Macedonia in the total population and the most diagnosed cancer in men. In 2020, lung cancer was the most frequently diagnosed cancer in Macedonia, with 14.9 % of new cancer cases, while worldwide, and in Southern Europe, it was the second most commonly diagnosed cancer with 11.4 % and 11.0 %, respectively, and the third most frequent in EU-27 with 10.8 %. Malignant neoplasm of the bronchus and lung was the most common cancer diagnosis in 2020 in the male population in Macedonia and globally, with a higher incidence in Macedonia (21 %) compared to the world (14.3 %). In terms of cancer morbidity in 2020 in the female population, lung cancer ranks fourth in Macedonia (7.2 %) and third in the world (8.4 %), EU-27 (8.4 %) and Southern Europe (7.1 %). Malignant neoplasm of the bronchi and lungs was the leading cause of cancer death in 2020. Concerning mortality, malignant neoplasm of the bronchus and lung was the leading cause of cancer death in 2020. Lung cancer mortality in Macedonia in 2020 was higher (23.3% of cancer deaths) compared to the world (18%), EU-27 (20.3%) and Southern Europe (20.2%).

As to cervical cancer, from 2011 to 2020, with 5.6 %, it was the fifth most common cancer diagnosis among women in Macedonia (excluding non-melanoma skin cancer). In 2020, cervical cancer was the fourth most frequently diagnosed cancer in women worldwide (6.5%) and the fifth most commonly diagnosed cancer in the female population in Macedonia (3.3%). In overall cancer statistics, in terms of cancer incidence in 2020, cervical cancer ranks 15th in Macedonia (1.5 %), 8th in the world (3.1 %), 20th in EU-27 (1.0 %) and 21st in Southern Europe (0.95 %). Concerning deaths of cancer in 2020, cervical cancer ranks 16th in Macedonia (1.5 %), 9th in the world (3.4 %), 20th in EU-27 (1.1 %) and 21st in Southern Europe (0.88 %).

Regarding brain cancer (C71), it was the 13th most common cancer diagnosis in Macedonia from 2011 to 2020, with 2.4 % of the total reported cases, 11th in men (2.5 %) and 12th in women (2.25 %). In 2020, brain, central nervous system cancer (C70-C72) was the 9th most frequently diagnosed cancer in Macedonia (4.0%), while it was 20th in the world (1.6%), 16th in the EU-27 and Southern Europe with 1.5% and 1.6%, respectively. In terms of mortality in 2020, brain cancer was the 7th leading cause of cancer death in Macedonia (6.0 %), 13th worldwide (2.5 %), 12th in EU-27 (2.7 %) and 11th in Southern Europe (2.9 %).

As can be seen from the comparison, cervical cancer has a lower incidence and mortality in Macedonia than in the world but a higher incidence and mortality compared to the EU-27 and Southern Europe. Lung and brain cancers have a higher incidence and mortality in Macedonia than in all other compared regions: the world, EU-27 and southern Europe.

These results indicate that it is rational to adopt strategies which can contribute to better management of malignant diseases in Macedonia. One of those strategies is the introduction of new radiopharmaceuticals in nuclear medicine practice, which would promote a more personalized approach to cancer management. Radiopharmaceuticals based on copper-64 are very promising due to the unique properties of this radionuclide that are complementary for diagnostic and/or therapeutic purposes. $^{64}\text{Cu}[\text{Cu}(\text{ATSM})]$ is one of the most researched ^{64}Cu -radiopharmaceuticals. It has been used in clinical studies to detect hypoxia in solid malignant tumors. $^{64}\text{Cu}[\text{Cu}(\text{ATSM})]$ PET imaging was chosen as the technique of choice for the detection of hypoxia in these tumors, due to the physical inaccessibility of using invasive methods. Hypoxia is a common and important feature of solid malignancies and is typically associated with malignant progression, metastasis, resistance to chemotherapy and/or radiotherapy, recurrence and poor prognosis. The detection of tumor hypoxia is therefore of particular importance for optimizing the treatment strategy and improving the overall prognosis. PET is a noninvasive method for measuring hypoxia, highly sensitive and directly quantitative. Quantitative data on the expression of hypoxia is useful to determine before chemotherapy and radiotherapy in order to choose the appropriate treatment and optimize therapeutic doses. (Liu et al., 2020; Lopci et al., 2016). The advantage of introducing copper-64-PET into clinical practice is the possibility of providing more individualized and optimized cancer treatment, thereby improving clinical outcomes and rationalizing therapy costs.

5. CONCLUSIONS

Within the framework of the preliminary analysis, which is the first phase of the feasibility study for establishing the production of copper-64 radioisotope, a review of statistical data regarding malignant diseases was performed. The results of the cancer statistics review indicate that it is justified to implement strategies that could contribute to reducing the incidence of solid malignancies in Macedonia and mortality due to them.

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