FDA Executive Summary

Prepared for the November 7, 2023, Meeting of the Radiological Devices Advisory Panel of the Medical Devices Advisory Committee

Discussion and Recommendations for the Classification of Blood Irradiators for the Prevention of Metastasis

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1. Introduction

As required by Section 513(b) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the Food and Drug Administration (FDA) is convening the Radiological Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of blood irradiators intended for use in the irradiation of intra-operatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis (hereafter, "blood irradiator(s)" or "blood irradiators for the prevention of metastasis"), a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the appropriate regulatory classification to provide reasonable assurance of safety and effectiveness of blood irradiators for the prevention of metastasis. These are a subset of devices current cleared under the product code "MOT". The device names and associated product codes are developed by the Center for Devices and Radiological Health (CDRH) in order to identify the generic category of a device for FDA. While most of these product codes are associated with a device classification regulation, some product codes, including "MOT" remain unclassified.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of blood irradiators for the prevention of metastasis. The Panel will discuss whether the blood irradiators for the prevention of metastasis should be classified into Class III (subject to General Controls and Premarket Approval), Class II (subject to General and Special Controls) or Class I (subject only to General Controls). If the Panel believes that classification into Class II is appropriate for the blood irradiators for the prevention of metastasis, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1 Current Regulatory Pathways

Blood irradiators for the prevention of metastasis are a pre-amendments, unclassified device type. This means that this device type was marketed prior to the enactment date of the Medical Device Amendments of 1976 on May 28, 1976, but was not classified by the original classification panels. Currently, these devices are being regulated through the 510(k) pathway, and are cleared for marketing if their intended use and technological characteristics are "substantially equivalent" to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product code.

1.2 Device Description

Blood irradiators for the prevention of metastasis is a device type intended for use in the irradiation of intra-operatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis. Blood lost during surgery is collected using a suction device and may be processed or filtered before being irradiated to prevent the proliferation of cancer cells that may be present. The blood is then reinfused to the same patient either intra-operatively or post-operatively in an autologous blood transfusion. Blood irradiation of intra-operatively salvaged blood in order to prevent metastasis does not currently appear to be a widely used technique.

Blood irradiators are designed to deliver a desired dose of ionizing radiation to *ex vivo* blood or blood products. While FDA-cleared blood irradiator devices use one of two radiation emitting methods, a radioisotope source (e.g., Cobalt-60 or Cesium-137) or an x-ray tube, this classification panel is only focused on blood irradiator devices that use x-ray tubes for the prevention of metastasis.

In general, blood irradiators have a cabinet design, with a shielded irradiation chamber, and a high voltage power supply. They have an access panel or mechanism to access the irradiation chamber, a user interface (either manual or electronic), and additional operator controls. Electrically powered timers are used to set a predetermined exposure time for the sample. Devices may include a battery backup system in case of power interruption. The irradiator sample chambers vary in dimension, and the devices include safety interlocks so the door or access panel cannot be opened when the x-ray tube is irradiating the blood, or blood components in the sample chamber. The device may contain a graphical user interface that displays information at the time of irradiation and often contains software so that data can be recorded digitally.

X-ray based blood irradiators utilize a conventional x-ray tube system enclosed in a lead shielded container. In some cases, the x-ray tube is capable of emitting x-rays in a 360 degree output around its cylindrical design. The devices may contain a mechanism to rotate the sample in front of the source to ensure all products being irradiated receive the minimally required radiation dose. X-ray emitting devices have a mechanism to cool the x-ray tube, control the kV and mA of the x-ray tube, and methods to filter the x-ray beam. Blood irradiators that use x-ray tubes are considered radiation-emitting electronic products subject to the Electronic Product Radiation Control (EPRC) requirements of the FD&C Act, and its implementing regulations. This includes compliance with certain portions of 21 CFR Chapter I, Subchapter J, including the FDA performance standards found in 21 CFR 1020.40 for cabinet x-ray systems.

2. Regulatory History

Blood irradiators are pre-amendments devices, meaning that they have been in commercial distribution prior to the enactment date of the Medical Device Amendments of 1976, on May 28, 1976. In 2012, a Panel was convened to discuss the proposed classification into Class II of blood irradiators in product code “MOT” intended for the use in the irradiation of blood and blood products to inactivate T-lymphocytes for the prevention of graft-versus-host disease. The panel agreed with the proposed Class II classification. The classification of blood irradiators for the prevention of metastasis was not discussed.

FDA has cleared two blood irradiators for the prevention of metastasis. The Raycell X-Ray Blood Irradiator manufactured by MDS Nordion was the first device cleared by FDA on May 26, 2005. The FDA determined that the Raycell X-Ray Blood Irradiator was substantially equivalent to pre-amendment blood irradiator devices. Table 1 below shows the manufacturers, device names, and associated 510(k) submission numbers for FDA-cleared blood irradiator devices for the prevention of metastasis.

Table 1: 510(k) Clearances for Blood Irradiators for the Prevention of Metastasis

510(k) Number	Trade Name	Manufacturer
K051065	Raycell X-Ray Blood Irradiator	MDS Nordion
K161324	Raycell Mk2	Best Theratronics Limited

3. Indications for Use

The Indications For Use (IFU) statement identifies the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

Blood irradiators for the prevention of metastasis have been cleared for the following indication:

> The [device] is intended for use in the irradiation of intra-operatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis.

3.1 Relevant Historical Agreements and Important Guidance Documents

Blood Irradiators as medical devices are among a few medical devices that are jointly regulated by the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH). How, when and which FDA center regulates blood irradiators is discussed in an Intercenter Agreement outlined below.[1]

Intercenter Agreement Between the CBER and CDRH

On October 31, 1991, a document that outlined the working relationships that exist between CBER and CDRH for certain categories of medical devices or specified medical devices was ratified. CDRH was designated the lead center in the FDA for regulating medical devices and radiation related medical devices to ensure their safety and effectiveness. CDRH uses the device authorities of the FD&C Act and the EPRC requirements of the FD&C Act, as well as any other authorities delegated to it as appropriate, for devices regulated in that Center. CBER was designated the lead Center in the FDA for regulating certain medical devices utilized in or indicated for the collection, processing, or administration of biological products to ensure their safety and effectiveness and will use authorities under the Public Health Services Act (the PHS Act).

[1] "Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health." Effective October 31, 1991. Available at: https://www.fda.gov/combination-products/jurisdictional-information/intercenter-agreement-between-center-biologics-evaluation-and-research-and-center-devices-and

Irradiators intended for use in the inactivation of immunologically active cells in whole blood, red blood cells and platelets are regulated by CDRH with consultation by CBER on the safety and effectiveness of the irradiated product.

Irradiators intended for use in the in-process inactivation of HIV viruses or other pathogens in all blood products, licensed biological products, or analogous products will be regulated by CBER with consultation by CDRH.

CBER Guidance on Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products
On July 22, 1993, CBER published recommendations regarding license amendments and procedures for gamma irradiation of blood products for all registered blood establishments.[2] This document is focused on the use of irradiation to reduce the number of viable T lymphocytes for the prevention of graft-versus-host disease and not for the irradiation of intraoperatively salvaged blood for cancer patients undergoing surgery to assist in the prevention of metastasis. Although this document was written for gamma-emitting radioisotope blood irradiators, x-ray based blood irradiators can perform the same function as the radioisotope irradiators and this document has been adopted for x-ray based blood irradiation procedures.

4. Clinical Background

4.1 Disease Characteristics

Cancer is one of the leading causes of death globally and the second leading cause of death in the United States, with approximately 1.6 million new cancer cases reported and 602,347 deaths in 2020.[3] It can occur almost anywhere in the body and is the result of aberrant processes including cell division, cell growth, and cell death which can lead these abnormal cells to form tumors. Tumors may spread from their original location into other tissues within the body and form new tumors, a process called metastasis. Patients with metastatic cancer, or that which has spread from the original (primary) tumor, generally have a worse prognosis than those with non-metastatic cancer. Metastatic cancer is often treatable, but not always curable.

Tumor cells can leave the original tumor via the vascular or lymphatic systems and have been found in the circulating blood. Patients with cancer may undergo surgery to remove their tumor, or tumors, and they may also undergo surgeries for other reasons during their cancer treatment. During oncologic surgery, patients may experience significant blood loss and require a blood transfusion. As an alternative to an allogenic

[2] "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products". Dated July 22, 1993. Available at: https://www.fda.gov/files/vaccines%2C%20blood%20&%20biologics/published/Recommendations-Regarding-License-Amendments-and-Procedures-for-Gamma-Irradiation-of-Blood-Products.pdf

[3] U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in June 2023.

blood transfusion, salvaged blood from the cancer patient can be re-infused into the cancer patient during surgery or immediately after surgery. The salvaged blood can be passed through a leukocyte reduction filter to reduce the concentration of nucleated white blood cells. Nucleated white blood cells and tumor cells are more sensitive to ionizing radiation than other blood components. This sensitivity difference can be exploited with radiation to remove activated T-cells to prevent transfusion-associated graft versus host disease or kill tumor cells within salvaged blood.

4.2 Patient Outcomes

The primary outcome measure for patients with cancer is overall survival. Patient outcomes following the irradiation of intraoperatively salvaged blood from cancer patients undergoing surgery to assist in the prevention of metastasis may also include risk of postoperative infections, tumor recurrence, or spread of cancer (i.e., metastasis).

4.3 Currently Available Treatment

Malignant cells have been seen in blood collected intraoperatively.[4] To determine whether blood should be salvaged intraoperatively from cancer patients undergoing surgery, the following are considered: risk of major intraoperative bleeding, necessity of transfusion, availability of allogenic blood, clinical presentation and standard of care, underlying condition or disease, patient preference and informed consent, patient medical history, surgeon preference. For most patients, allogenic blood transfusion (transfusion of compatible blood from one individual to another) is considered the standard treatment for blood loss during surgery or for low postoperative hemoglobin levels. For the intraoperative blood salvage, “cell saver” or “cell recovery” technologies separate, wash, and concentrate salvaged red blood cells. The blood is typically reinfused to the patient using microaggregate filters or leukocyte depletion filters. Leukocyte depletion filters are cleared for the removal of white blood cells from blood components – they have the ability to remove cancer cells in addition to leukocytes.[5]

Alternatives to intraoperative cell salvage include preoperative donation by the patient undergoing surgery (autologous donation) or other intraoperative techniques such as hemodilution or postoperative salvage. These alternative methods may be preferentially used for patients where blood transfusion is not an option, such as those with religious reasons or where there is an underlying safety concern. Additionally, this may be used as a strategy to reduce or avoid allogenic transfusion. The primary objection to the use of intraoperatively salvaged blood in oncologic patients undergoing surgery is the possibility that malignant cells in the operative field will be re-transfused and result in tumor recurrence and metastasis.[6] Active malignancy is considered a relative contraindication to intraoperative blood salvage, though this may be seen as controversial with no compelling evidence to suggest an association with adverse

[4] Kumar N, et.al. Flow cytometric evaluation of the safety of intraoperative salvaged blood filtered with leucocyte depletion filter in spine tumour surgery. Ann Surg Oncol. 2014 Dec;21(13):4330-5. Epub 2014 Jul 29.
[5]Catling S, Williams S, Freites O, Rees M, Davies C, Hopkins L. Use of a leucocyte filter to remove tumour cells from intra-operative cell salvage blood. Anaesthesia. 2008;63(12):1332-8. doi: https://doi.org/10.1111/j.1365-2044.2008.05637.x..

outcomes.[12,7,8]

4.4 Risks

FDA has identified the following risks to health associated with blood irradiators for the prevention of metastasis:

Table 2: Risks to Health and Explanatory Descriptions/Examples for Blood Irradiators for the Prevention of Metastasis

Identified Risk	Description/Examples
Presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered	• Incorrect dose of radiation identified to be effective may result in tumor cell survival leaving proliferative (able to function, grow, and divide) tumor cells present in the blood. • Device malfunction or lack of adequate maintenance, dosimetry or of quality assurance checks, could lead to improper dose of radiation delivered to the blood or blood components resulting in incomplete tumor cell death and presence of proliferative tumor cells in the blood. • Operator error, including improper loading of the sample canister containing the blood or blood component, incorrect time entered into the user interface resulting in improper dose of radiation delivered leading to presence of proliferative tumor cells in the blood.
Worsened control of oncologic disease or patient prognosis	• Irradiating blood or blood component may cause an immune response that negatively impacts cancer outcome or patient recovery or survival.[9]
Damage to blood components from radiation	• Irradiation of whole blood and red blood cells causes damage to red blood cells and lymphocytes within the blood.[10] Radiation damages the membrane of red

[7] https://www.uptodate.com/contents/surgical-blood-conservation-blood-salvage#H380732602. Accessed July 16, 2023.

[8] Zaw AS, Bangalore Kantharajanna S, Kumar N. Is Autologous Salvaged Blood a Viable Option for Patient Blood Management in Oncologic Surgery? Transfus Med Rev. 2017;31(1):56-61. Epub 20160621. doi: 10.1016/j.tmrv.2016.06.003. PubMed PMID: 27421661.

[9] Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev. 2018;32(19-20):1267-84. doi: 10.1101/gad.314617.118. PubMed PMID: 30275043; PubMed Central PMCID: PMC6169832.

[10] "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products". Dated July 22, 1993. Available at: https://www.fda.gov/files/vaccines%2C%20blood%20&%20biologics/published/Recommendations-Regarding-License-Amendments-and-Procedures-for-Gamma-Irradiation-of-Blood-Products.pdf

	blood cells leading to higher concentrations of potassium in plasma, hemolysis (destruction of red blood cells), and affects red cell viability.
Unintended radiation exposure to the operator and public	• Device malfunction, lack of adequate maintenance, or safety control or interlock failure could allow the operator to access the radiation source resulting in physical injury and/or exposure of the operator or other nearby persons to radiation. Exposure to ionizing radiation has been shown to increase cancer risk. • Insufficient presence of safety controls or interlocks within irradiator design may allow x-ray tube to generate x-rays when it should be shut off, resulting in unintended exposure.
Electrical shock or burn	• Electrical malfunction of the device or user contact with an energized portion may result in electrical shock or burns. This can occur when there are insufficient or malfunctioning safety controls or interlocks.
Delayed or lack of retransfusion of irradiated blood or blood component	Use of device inherently adds time to re-transfusion procedure. Device malfunction, or operator error could add additional delay or risk of giving salvaged blood that was not irradiated. • Delayed re-transfusion of the blood or blood component to the patient could occur due to device malfunction, including from mechanical, electrical, or software malfunctions, or use error. • Operator error or device malfunction could lead to blood not being irradiated or being irradiated to incorrect dose, both of which would not kill tumor cells. In addition, operator error or device malfunction could result in in over irradiation, thereby impairing blood function. These could lead to the blood not being suitable for patients and not being given for re-transfusion.
Mechanical or crush injury	• Mechanical or crush injury may result from shielded doors being closed, impinging on operator.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by blood irradiators for the prevention of metastasis and whether any other risks should be included in the overall risk assessment of the device type.

5. Literature Review

As radioisotope sources and x-ray sources are known to produce ionizing radiation that damages DNA and stops the proliferation of cancer cells, both types of blood irradiators (radioisotope and x-ray based) were included in the literature search to inform the risks to health and effectiveness data for blood irradiators intended for the irradiation of intraoperatively salvaged blood for the prevention of metastasis.

5.1 Methods

A systematic literature review was conducted, in an effort to gather any published information regarding the safety and effectiveness of blood irradiators for the prevention of metastasis. Since the FDA-cleared blood irradiators in product code MOT are similar in design and function to those intended for the prevention of metastasis, any literature referencing use of a blood irradiator was analyzed. Two electronic databases (Embase and PubMed) were searched for studies published from January 1, 2002, to April 20, 2023. Additionally, a manual search was undertaken to identify additional relevant articles. References from original papers and abstracts, reviews, systematic reviews, and meta-analyses were checked to identify any additional studies. The search strategy for each database, article retrieval and selection process, and review inclusion criteria is given in Appendix A. Full references for articles mentioned within the literature review section of this document can be found in Appendix D.

5.2 Results

The search yielded 487 records, with twelve identified as duplicates. In total, 475 unique records were identified from the database searches and these articles were screened during the title/abstract review. After excluding 439 records that were not relevant to the review at the title/abstract level, 36 full texts were reviewed and 10 were found to meet inclusion criteria and were determined to be relevant to the safety and effectiveness of blood irradiators used to prevent metastasis. The number of each excluded criterium is also summarized in the flow diagram in Appendix B.

Of the 10 articles found to meet inclusion criteria, there were no randomized controlled trials. None of the 10 articles specifically mentioned the use of either of the blood irradiators indicated for the prevention of metastasis by device name or company name (Table 1). All studies were performed outside of the United States, with the three observational studies being performed in Germany, Switzerland, and Brazil.

The evidence base of the review comprised:

- three observational studies:
    - Weller et al. 2021(retrospective cohort study)

    - Poli et al. 2008 (uncontrolled case series)
    - Beck-Schimmer et al. 2004 (uncontrolled case series);
- four narrative reviews (included here due to the dearth of evidence on the topic)
    - Fisher et al. 2019, Trudeau et al. 2012, Hansen et al, 2003, and Hansen et al. 2002, and
- three expert recommendations.

Of the observational studies, only two included re-transfusion of the irradiated salvaged blood to the patient, Beck-Schimmer et al. and Weller et al. (Reference 1, 2) and of those, only one followed patients for tumor recurrence. While Weller et al. followed patients for recurrence after receiving irradiated cell-salved blood, patients received transfused allogenic red blood cells, fresh frozen plasma, and platelets in addition to the salvaged blood (Reference 2). The types of cancer that patients retransfused with irradiated blood differed between the two studies: hepatocellular carcinoma (Weller et. al) and uterine or ovarian cancer (Beck-Schimmer et al.). Patients' mean ages in the observational studies ranged from 58 to 63 years. Gender distribution in one study was 78.4% male, while one study included only women (focus on gynecological cancers) and the other only men (focus on prostate cancer). The retrospective cohort study had a follow-up period >2 years, while the two uncontrolled case series had 24-hour follow up only. Sample sizes ranged from 9-51.

One *in vitro* study by Hansen et al. 1999 (Reference 3) was referenced in almost all literature returned as being the basis for the recommendation that irradiation at 25 – 50 Gy resulted in removal of viable tumor cells from intraoperatively salvaged blood. This study was not identified within the systematic literature review because it fell outside the timeframe search (2002-2023), and was an *in vitro* study, but was evaluated because of its multiple citations.

Summaries of the 10 articles identified in the literature search and the Hansen et al. 1999 paper are included Appendix C as are the full details on the observational studies reviewed. No relevant preclinical *in vivo* studies were located in the literature search or searches of clinical trial registries. Of the four clinical trials related to blood salvage in cancer surgery at clinicaltrials.gov and one in a search of the World Health Organization's International Clinical Trials Registry Platform, none included irradiation.

5.3 Adverse Events Associated with Blood Irradiators for the Prevention of Metastasis

None of the articles evaluated discussed risks or performance issues related to any identified blood irradiator device used for the prevention of metastasis.

While not specifically an adverse event, multiple papers identified that irradiating blood took additional time. Hansen et al. 1999 and 2003 noted that the irradiation to 50 Gy would take approximately 6-15 minutes, and the Weller et al. 2021 paper indicated that

the duration from irradiation to retransfusion was <20 minutes at their institution. Weller notes that logistics and procedures are essential to avoid any delays in patient treatment through the irradiation procedure.

5.4 Effectiveness Associated with Blood Irradiators for the Prevention of Metastasis

Only one article examined the effect of irradiation on metastasis (Weller et al. 2021). However, the effect of salvaged blood irradiation on tumor recurrence could not be definitively evaluated and there was no difference in tumor recurrence between the groups that received autologous blood with or without radiation. Additionally, all patients received allogenic transfusions of red blood cells, fresh frozen plasma, and platelets.

Two studies (Hansen et al. 1999, Poli et al. 2008) provided evidence indicating that blood irradiation could damage tumor cells such that they were no longer proliferative or showed evidence of DNA metabolism, or that tumor cells were not detected after washing, filtration, and irradiation, but these studies did not examine the *in vivo* prevention of metastasis in patients who received an autologous transfusion after irradiation.

5.5 Overall Literature Review Conclusions

As noted above, none of the articles specifically mentioned the use of either of the blood irradiators indicated for the prevention of metastasis by device name or company name. The systematic literature review returned only 10 articles, with no randomized controlled trials related to this topic located in the publication range searched (January 1, 2002 - April 20, 2023). All studies were performed outside the United States, limiting the generalizability to the intended use population without additional information.

The data to support effectiveness of irradiation of intraoperatively salvaged blood to prevent metastasis is sparse. Only two studies retransfused irradiated blood into patients. While the Weller et al. (Reference 2) study indicated that the difference in the number of patients with tumor recurrence between groups was not significant, only 10 patients out of the 51 (19.6%) studied had a recurrence during the follow-up period and the numbers in each treatment group and the number in each group that had a recurrence were small ($\leq$4 per treatment group). All patients involved in the study received transfusion of allogenic red blood cells, platelets, and fresh frozen plasma with the number of transfused cells not differing significantly between study arms. Additionally, because the study was retrospective and, therefore, as all specifics related to patients treated (e.g., date of treatment, extent of liver disease) are not identified in the paper, it is unclear if the data are generalizable to the intended patient population due to bias that may have been introduced in how the treatment was performed. It is unclear if there was possible patient selection bias as before 2017, the anesthesiologists in charge were able to decide

whether the salvaged blood was irradiated before transfusion, while all blood after 2017 was irradiated. This difference could confound the results as the anesthesiologist in charge likely differed across the surgeries and there were no clear criteria for patient selection. The publication by Beck-Schimmer et al. did not evaluate the effect of blood irradiation on the prevention of metastasis, instead looking for markers of immunological inflammatory response.

Two studies (Hansen et al. 1999, Poli et al. 2008) provided evidence indicating that blood irradiation could damage tumor cells such that they were no longer proliferative or showed evidence of DNA metabolism, or that tumor cells were not detected after washing, filtration, and irradiation, but these studies did not examine the *in vivo* prevention of metastasis in patients who received an autologous transfusion after irradiation. Poli, et al. looked for the presence of tumor cells in blood collected prior to surgery and from the surgical field, with the blood from the surgical field being subjected to a combination of additional processing steps (washing, filtration, and irradiation). While the authors indicate that their data show no presence of tumor cells after the combination of washing, filtration, and irradiation, inconsistent results were found across samples from the same patient after each processing step, limiting the ability to draw a conclusion on effectiveness of irradiation. The Hansen et al. paper may provide some evidence that irradiation can kill tumor cells, the underpinning of the field of radiation oncology, but as an *in vitro* study, does not show that such tumor cell kill result in a prevention of metastasis.

The three professional guidelines located that addressed use of irradiation in intraoperative blood salvage during cancer surgery reference the 1999 Hansen et al. article as the principal evidence in support of the approach. In all three, strength of evidence was rated as weak and in the C range, reflecting lack of any randomized controlled trials, uncertainty in the risk to benefit balance and that other alternatives may be equally reasonable.

No adverse events were reported or addressed in any of the literature returned from the systematic search and there was no information regarding performance of the blood irradiator devices used provided in any of the articles.

Literature-reported doses used for blood irradiators for intraoperatively salvaged blood to assist in the prevention of metastasis in cancer patients ranged from 25-50 Gy based off of the single 1999 in vitro study by Hansen et al. Of the recommendations from professional societies, one recommended the use of 25 Gy, one 50Gy, and one did not discuss radiation dose, indicating a lack of consensus on adequate dose. From the information provided in the literature review, it is unclear what dose of radiation could effectively be used to irradiate intraoperatively salvaged blood to prevent metastasis, or if that dose would be the same for all cancer types and all surgical procedures.

Overall, the quality of the evidence from the systematic literature review is low. Available evidence is inadequate to draw any definitive conclusions about the safety or

effectiveness of the use of blood irradiators to irradiate intraoperatively salvaged blood for the prevention of metastasis.

6. Risks to Health Identified through Medical Device Reports (MDRs)

6.1 Overview of the Medical Device Reporting (MDR) System

The Medical Device Reporting (MDR) system provides FDA with information on medical device performance from patients, health care professionals, consumers, and mandatory reporters (manufacturers, importers, and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type, and
- Detect actual or potential device problems used in a "real world" setting/environment.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2 MDR Data: Blood Irradiators for the Prevention of Metastasis

Individual MDRs for blood irradiators for the prevention of metastasis are reported through FDA's Manufacturer and User Facility Device Experience (MAUDE) database, which houses mandatory reports from medical device manufacturers, importers, and user facilities, as well as voluntary reports from entities such as health care professionals, patients and consumers.

A search of MDRs was performed, without a date range, to include all MDRs received under the product code MOT up to September 25, 2023. Product code MOT covers blood irradiators intended to irradiate blood to inactivate T-lymphocytes for the prevention of graft-versus-host disease and blood irradiators intended for the prevention of metastasis. As radioisotope sources and x-ray sources are known to produce ionizing

radiation that damages DNA and stops the proliferation of cancer cells, both types of blood irradiators (radioisotope and x-ray based) were included in the MDR analysis to inform the risks to health and effectiveness data for blood irradiators intended for the irradiation of intraoperatively salvaged blood for the prevention of metastasis. The two blood irradiators cleared for the prevention of metastasis also have similar design and function as the blood irradiators cleared to inactivate T-lymphocytes for the prevention of graft-versus-host disease and, therefore, all MDRs were considered to provide relevant information toward understanding device hardware performance, detect potential hardware and software-related safety issues, and contribute to benefit-risk assessments of blood irradiators for the prevention of metastasis.

The MDRs were reviewed to ensure that any adverse events related to the use of the blood product in patients would be relevant to the devices being classified. The search resulted in the identification of seven unique MDRs for inclusion in this analysis. Out of the seven, one MDR was for a magnetic resonance imaging (MRI) coil that was miscategorized, and another MDR that described the malfunction of film used to identify the dose of radiation delivered. Therefore, these two MDRs were not included in this analysis, leaving five MDRs related to blood irradiators. Of the five MDRs specific to blood irradiators, two contained no narrative and could not be analyzed. One MDR (2009) was a suggestion that manufacturers should upgrade all devices to provide an audible alarm or computer generated message/alert to designate a serious mechanical failure as the current devices were dependent on the operator watching an indicator light on the device instrument panel. The remaining two analyzable MDRs were related to low x-ray tube output which may have resulted in less than 15 Gy being delivered to all locations within the device canister. The incorrect dose was not detected by radiation film indicators within the inside canister due to the location of the film. In one instance, a leak from the coolant systems caused corrosion and leached inside the x-ray chamber. The corrosive material deposited on the filter and partially blocked the beam. In the second instance, the root cause appeared to be an incorrect signal being sent to the power supply, either due to a faulty control board or due to a damaged or corroded cable connection between the control board and power supply.

Overall, the MDR analysis shows few device malfunctions over the lifetime of use for these devices.

In addition to analysis of the MDRs, an analysis of Accidental Radiation Occurrences was performed. Manufacturers of radiation-emitting electronic products must report to FDA all accidental radiation occurrences reported to or otherwise known to the manufacturer which arise from the manufacturing, testing, or use of the product. This requirement is outlined within 21 CFR 1002.20. Our analysis uncovered no Accidental Radiation Occurrence reports for product code MOT, including blood irradiators for the prevention of metastasis.

7. Recall History

7.1 Overview of Recall Database

The Medical Device Recall database contains Medical Device Recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date ("create date") identified on the database indicates the date FDA classified the recall, it does not necessarily mean that the recall is new.

7.2 Recall Results: Blood Irradiators for the Prevention of Metastasis

A search of recalls was performed, without a date range, to include all recalls received under the product code MOT up to September 27, 2023. Product code MOT covers blood irradiators intended to irradiate blood to inactivate T-lymphocytes for the prevention of graft-versus-host disease as well as blood irradiators intended for the prevention of metastasis. The blood irradiators under MOT have similar design and function, and therefore recalls were considered to provide relevant information toward understanding device hardware and software performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. Any recalls related to the use of the blood product in patients were specially reviewed for relevancy to the blood irradiators for the prevention of metastasis being classified.

A total of one recall has been reported to date for devices with the product code MOT. The recall was classified as a Class II recall[11] and a summary provided below.

- Z-2251-2016: This class II recall is for an x-ray based blood irradiator intended for prevention of graft-versus-host disease, that did not comply with the associated performance standards within 21 CFR Subchapter J Radiological Health.

8. Summary

In light of the information available, the Panel will be asked to comment on whether blood irradiators for the prevention of metastasis meet the statutory definition of a Class III device in accordance with section 513(a) of the FD&C Act, that is:

[11] Recalls are classified into a numerical designation (I, II, or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled. A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, AND
- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or the device presents a potential unreasonable risk of illness or injury.

or whether this device type would be more appropriately regulated as Class II, in which:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND
- there is sufficient information to establish special controls to provide such assurance.

The literature search performed did not identify any documented risks to health, only noting the time needed to irradiate the blood which would be an additional step added to any intraoperative blood salvage and surgical procedure. The risk of inadequate radiation dose delivery to the blood was identified based on adverse event reports received by the FDA, but not all risks may be known. Given the limited available information for blood irradiators intended for the prevention of metastasis, FDA believes insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of their safety and effectiveness.

Additionally, the device presents a potential unreasonable risk of illness or injury based on the limited clinical information that is available. There is a lack of evidence supporting effectiveness and a large amount of uncertainty surrounding the patient benefit from the device. Although limited information was available, based on the literature search conducted and the evidence obtained from review of the MAUDE database, FDA has identified the risks of presence of proliferative tumor cells with the use of blood irradiators for the prevention of metastasis and potential increase in cancer recurrence or worsening of patient prognosis due to immunological response to irradiation or irradiated blood, among others. Active malignancy is considered a relative contraindication for the use of intraoperative blood salvage, with an absence of definitive evidence to suggest a lack of adverse outcomes such as metastasis.[12,13,14] There is also no definitive evidence showing that irradiation of intraoperatively salvaged blood is able to prevent metastasis in patients. From the information provided in the literature review, it is unclear what dose of radiation could effectively be used to irradiate intraoperatively salvaged blood to prevent metastasis, or if that dose would be the same for all cancer types and all surgical procedures. Therefore, FDA believes the risk of injury is unreasonable given the lack of probable benefit.

FDA proposes that blood irradiators intended to irradiate intra-operatively salvaged blood from cancer patients to prevent metastasis meet the statutory definition of a Class III device

[12] Waters JH, Yazer M, Chen Y-F, Kloke J. Blood salvage and cancer surgery: a meta-analysis of available studies. Transfusion. 2012;52(10):2167-73. doi: https://doi.org/10.1111/j.1537-2995.2011.03555.x.

[13] https://www.uptodate.com/contents/surgical-blood-conservation-blood-salvage#H380732602. Accessed September 27, 2023.

[14] Zaw AS, Bangalore Kantharajanna S, Kumar N. Is Autologous Salvaged Blood a Viable Option for Patient Blood Management in Oncologic Surgery? Transfus Med Rev. 2017;31(1):56-61. Epub 20160621. doi: 10.1016/j.tmrv.2016.06.003. PubMed PMID: 27421661.

because insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of their safety and effectiveness. Additionally, blood irradiators for this indication present a potential unreasonable risk of illness or injury based on the limited clinical information that has been obtained.

If the Panel does not agree that the blood irradiators for this indication meet the statutory definition of a Class III device, the Panel will be asked for input regarding whether the available scientific evidence supports a Class II determination with special controls, including which special controls could be established to mitigate the known risks to health associated with these devices. If the Panel supports classification into Class II, the Panel will further be asked to provide reasons for not recommending classification of the devices into Class III.

For the purposes of classification, FDA also considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

21 CFR 860.7(g)(1) further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into Class III."

8.1 Reasonable Assurance of Safety for Blood Irradiators Intended to Assist in the Prevention of Metastasis

According to 21 CFR 860.7(d)(1), "there is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a

device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

FDA has identified potential risks to health associated with blood irradiators to assist in the prevention of metastasis. These include the following:

Table 3: Risks to Health and Explanatory Descriptions/Examples for Blood Irradiators for the Prevention of Metastasis

Identified Risk	Description/Examples
Presence of proliferative malignant cells in re-transfused blood due to incorrect dose or improper dose of radiation delivered	• Incorrect dose of radiation identified to be effective may result in tumor cell survival leaving proliferative (able to function, grow, and divide) tumor cells present in the blood. • Device malfunction or lack of adequate maintenance, dosimetry or of quality assurance checks, could lead to improper dose of radiation delivered to the blood or blood components resulting in incomplete tumor cell death and presence of proliferative tumor cells in the blood. • Operator error, including improper loading of the sample canister containing the blood or blood component, incorrect time entered into the user interface resulting in improper dose of radiation delivered leading to presence of proliferative tumor cells in the blood.
Worsened control of oncologic disease or patient prognosis	• Irradiating blood or blood component may cause an immune response that negatively impacts cancer outcome or patient recovery or survival.[15]
Damage to blood components from radiation	• Irradiation of whole blood and red blood cells causes damage to red blood cells and lymphocytes within the blood.[16] Radiation damages the membrane of red blood cells leading to higher concentrations of potassium in plasma, hemolysis (destruction of red blood cells), and affects red cell viability.

[15] Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev. 2018;32(19-20):1267-84. doi: 10.1101/gad.314617.118. PubMed PMID: 30275043; PubMed Central PMCID: PMC6169832.

[16] "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products". Dated July 22, 1993. Available at: https://www.fda.gov/files/vaccines%2C%20blood%20&%20biologics/published/Recommendations-Regarding-License-Amendments-and-Procedures-for-Gamma-Irradiation-of-Blood-Products.pdf

Unintended radiation exposure to the operator and public	• Device malfunction, lack of adequate maintenance, or safety control or interlock failure could allow the operator to access the radiation source resulting in physical injury and/or exposure of the operator or other nearby persons to radiation. Exposure to ionizing radiation has been shown to increase cancer risk. • Insufficient presence of safety controls or interlocks within irradiator design may allow x-ray tube to generate x-rays when it should be shut off, resulting in unintended exposure.
Electrical shock or burn	• Electrical malfunction of the device or user contact with an energized portion may result in electrical shock or burns. This can occur when there are insufficient or malfunctioning safety controls or interlocks.
Delayed or lack of retransfusion of irradiated blood or blood component	Use of device inherently adds time to re-transfusion procedure and device malfunction, or operator error could add additional delay or risk of giving salvaged blood that was not irradiated. • Delayed re-transfusion of the blood or blood component to the patient could occur due to device malfunction, including from mechanical, electrical, or software malfunctions, or use error. • Operator error or device malfunction could lead to blood not being irradiated or being irradiated to incorrect dose, both of which would not kill tumor cells. In addition, operator error or device malfunction could result in over irradiation, thereby impairing blood function. These could lead to the blood not being suitable for patients and not being given for re-transfusion.
Mechanical or crush injury	• Mechanical or crush injury may result from shielded doors being closed, impinging on operator.

Some of the identified risks could occur from the reported device-related adverse events related to incorrect dose of radiation delivered to the blood or blood component due to low x-ray tube output. As the dose of radiation necessary to remove proliferative tumor cells is unclear, the effects on the blood are unknown. The literature review did not identify any articles that discussed risks or performance issues related to any identified blood irradiator device used for the prevention of metastasis. There is also no definitive evidence showing that irradiation of intraoperatively salvaged blood is able to

prevent metastasis in patients or that it does not trigger an immunological response that could worsen patient prognosis (promote recurrence or invasiveness, or surgical recovery). Given the limited reported clinical use of blood irradiators for the irradiation of intraoperative blood salvaged from cancer patients to assist in the prevention of metastasis, this list of risks may not be exhaustive.

The FDA will ask the Panel to comment on the risks to health identified and whether there are additional risks that should be considered for blood irradiators for the prevention of metastasis, or if any of the identified risks should be removed. Additionally, the FDA will ask the Panel whether the evidence demonstrates a reasonable assurance of safety for the use of blood irradiators intended to assist in the prevention of metastasis.

8.2 Reasonable Assurance of Effectiveness for Blood Irradiators for the Prevention of Metastasis

According to 21 CFR 860.7(e)(1), "there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

Based on the information we could collect, there is inadequate evidence to draw any definitive conclusions about the effectiveness of the use of blood irradiators to irradiate intraoperatively salvaged blood to assist in the prevention of metastasis in cancer patients undergoing surgery. The one observational study that included retransfusion of irradiated intraoperatively salvaged blood, contained a control arm, and followed patients for tumor recurrence, Weller et al. 2021, but only examined occurrence of metastasis in patients with one type of cancer, had a small sample size of ten patients across three arms, and all patients received transfusion of allogenic blood components. While infusion of salvaged blood did not increase tumor recurrence rates, there was also no reduction seen in patients receiving salvaged blood that had been irradiated. Salvaged blood was only irradiated at 50 Gy, and it is therefore unclear what dose of radiation is correct to use and if the dose would be the same for all cancer types. No definitive conclusion can be drawn on whether irradiation of intraoperatively salvaged blood prevents metastasis.

The FDA will ask the Panel whether there is a reasonable assurance of effectiveness for the use of blood irradiators for the prevention of metastasis.

8.3 Overview of Proposed Classification

As noted above, a device will be considered Class III if:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, AND

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

The literature search performed identified limited documented evidence of effectiveness. A number of risks to health have been identified based on adverse event reports received by FDA for the same and similar devices cleared in product code MOT. However, not all such risks may be known. Given the limited information for these devices, including on the acute and long-term effects, FDA does not believe that special controls can be identified to mitigate the known risks to health associated with these devices for the intended use of irradiating blood to prevent metastasis. Therefore, FDA believes that insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of these blood irradiators for the prevention of metastasis.

In addition, FDA believes that blood irradiators intended for the prevention of metastasis present a potential unreasonable risk of illness or injury. Although limited information is available, based on the literature search conducted and the evidence obtained from review of the MAUDE database, active malignancy is considered a relative contraindication for the use of intraoperative blood salvage, with an absence of definitive evidence to suggest a lack of adverse outcomes such as metastasis. There is also no definitive evidence showing that irradiation of intraoperatively salvaged blood is able to prevent metastasis in patients or that it does not trigger an immunological response that could worsen patient prognosis (promote recurrence or invasiveness, or surgical recovery). Therefore, FDA believes the risk of injury is unreasonable given the lack of probable benefit.
Based on the safety and effectiveness information gathered by FDA, we recommend that blood irradiators for the prevention of metastasis be regulated as Class III devices.

892.XXXX Blood irradiator for the prevention of metastasis.
(a) *Identification.* Blood irradiator devices for the prevention of metastasis are prescription devices used to deliver a controlled radiation dose to blood or components salvaged during surgery to assist in the prevention of metastasis in cancer patients. It is not intended to be used for cancer treatment or therapy.

(b) *Classification.* Class III (Premarket Approval)

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification for blood irradiators for the prevention of metastasis.

Appendix A: Literature Search Details

Table 1 summarizes the patients, interventions, comparisons, outcomes, timing, and settings (PICOTS) elements that informed the inclusion/exclusion criteria.

Table 1. PICOTS Eligibility of studies.

PICOTS	Inclusion Criteria	Exclusion Criteria
Population	cancer patients undergoing surgery and receiving intraoperatively salvaged blood that has been irradiated to assist in the prevention of metastasis	patients without cancer, cancer patients not undergoing surgery and receiving intraoperatively salvaged blood
Intervention	the irradiation of intra-operatively salvaged blood via x-ray or gamma (devices with MOT product code)	non-irradiation approach to treatment of salvaged blood, blood irradiation for prevention of transfusion-associated graft versus host disease, focus on killing T-lymphocytes only
Comparison	intra-operatively salvaged blood without irradiation, other comparator, no comparator	none
Outcomes	1. Metastasis after procedure at any time 2. Other potential health risks or device failure routes for blood irradiator devices. 3. Cancer recurrence in patients receiving autologous salvaged blood with or without irradiation at any given time	studies that do not report at least one outcome of interest
Timing	any	none
Setting	US and OUS	none
Study Design	any (RCT, cohort, case-control, cross-sectional, case series, case reports, systematic reviews, expert opinions, meta-analyses, laboratory studies, animal studies)	ex-vivo human or animal studies
Language	articles published in English	non-English language articles
Publication dates	January 1, 2002-April 20, 2023	for any included SLRs, ≥80% of the included studies in the SLR must have been published within this date range

Tables 2 and 3 depict search strategies from PubMed and EMBASE. Search strategies were generated using the intervention and condition of interest. The search strategy also utilized

Boolean operators and medical subject heading [MeSH] and Emtree thesaurus terms. Search strategies below included studies both inside and outside the United States.

Table 2. PubMed Search Strategy, April 20, 2023

Search Number	Query	Filters	Results
5	#1 AND#3	Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review, Humans, Other Animals, English, from 2002 - 2023	344
4	#1 AND #2 AND #3	Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review, Humans, Other Animals, English, from 2002 - 2023	2
3	cancer[tiab] OR metastasis[tiab] OR metastasized[tiab] OR "Neoplasm Metastasis"[Mesh]	Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review, Humans, Other Animals, English, from 2002 - 2023	190,262
2	"salvaged blood"[tiab:~3] OR "auto transfusion"[tiab] OR "cell salvage"[tiab:~3]	Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review, Humans, Other Animals, English, from 2002 - 2023	297

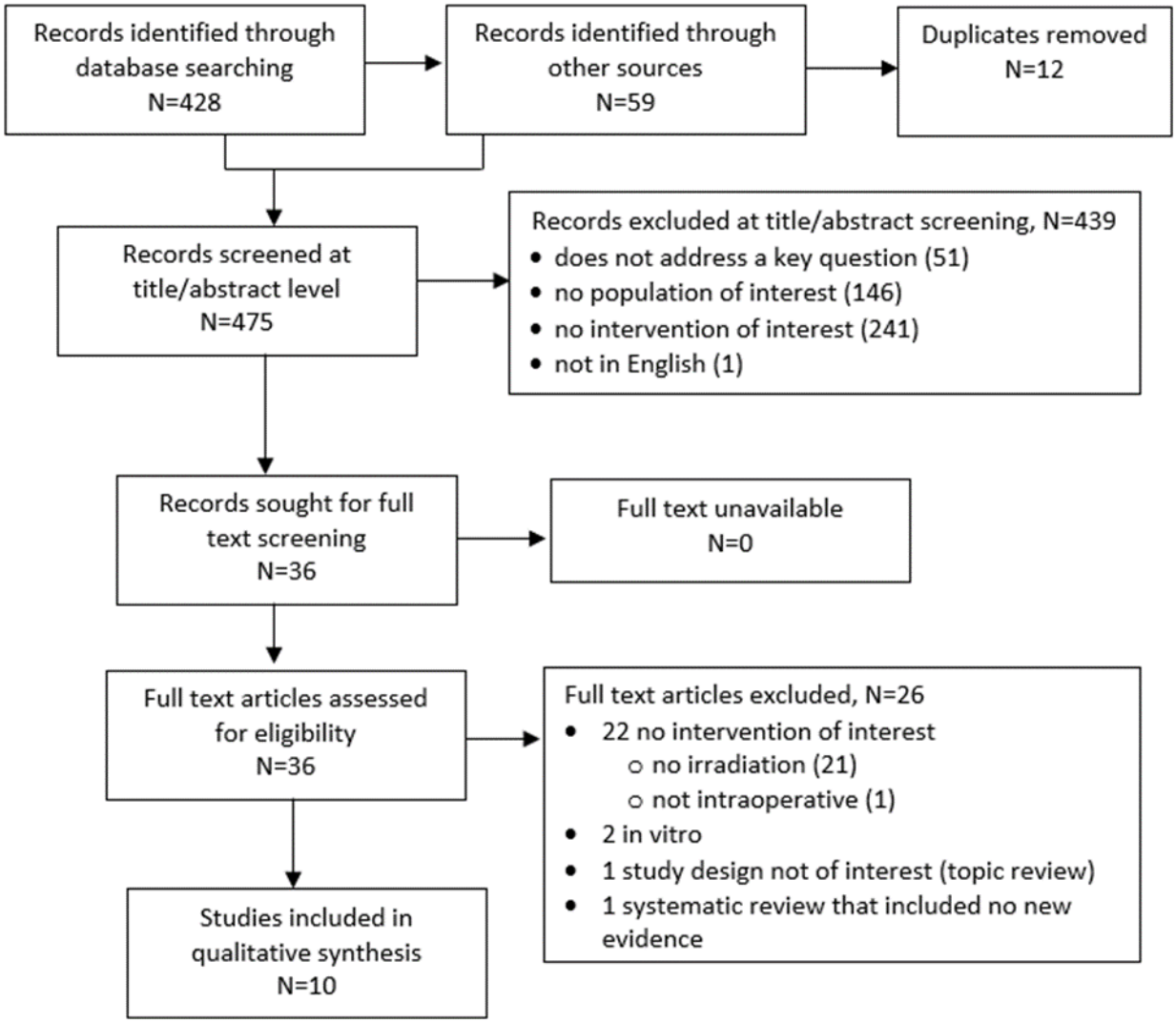
1	"blood irradiation"[tiab:~3] OR "blood irradiator"[tiab:~3] OR "blood irradiated"[tiab:~3] OR "blood radiation"[tiab:~3] OR ("Radiation"[Mesh] AND "Blood"[Mesh]) OR "blood radiation"[tiab:~3]	Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review, Humans, Other Animals, English, from 2002 - 2023	836

Table 3. Embase Search Strategy, April 20, 2023

No.	Query	Results
#9	#8 AND ([humans]/lim OR [animals]/lim) AND [english]/lim AND [2002-2023]/py	84
#8	#7 AND ('case control study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'observational study'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de OR 'systematic review'/de OR 'validation study'/de)	100
#7	#2 AND #3	608
#6	#5 AND ([humans]/lim OR [animals]/lim) AND [english]/lim AND [2002-2023]/py	2
#5	#1 AND #2 AND #3 AND ('case control study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'observational study'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de OR 'systematic review'/de OR 'validation study'/de)	3
#4	#1 AND #2 AND #3	11
#3	(blood NEAR/3 irradiat*) OR (blood NEAR/3 radiation) OR 'blood radiation'/exp	4900
#2	cancer:ti,ab OR metastasis:ti,ab OR metastasized:ti,ab OR 'metastasis'/exp	3359614
#1	(salvaged NEAR/3 blood) OR 'auto transfusion':ti,ab OR (cell NEAR/3 salvage)	2434

Appendix B: Flow Diagram of Systematic Literature Review Search Results

Figure 1. Literature flow figure



Appendix C: Summary of Systematic Literature Review for Intraoperatively Salvaged Blood Irradiated to Assist in the Prevention of Metastasis

The systematic literature review did not identify any literature that specifically referenced either of the two blood irradiators intended for the prevention of metastasis that have been cleared by FDA and mentioned in Table 1 of this document. The blood irradiators specifically identified use radioisotopes (Cesium-137 or Cobalt-60) and not an x-ray tube.

Observational Studies Summary
Characteristics and outcomes of included observational studies are summarized in Table 4. In a retrospective comparative study, Weller et al. analyzed incidence of tumor recurrence in patients ≥ 18 years of age who underwent liver transplantation for hepatocellular carcinoma between 2002 and 2018. (Reference 2) Tumor recurrence was compared for 28 patients who received autologous blood with irradiation during surgery, 11 who received autologous blood without irradiation, and 12 patients who did not receive transfusion of autologous blood. Per hospital policy, when intraoperative cell salvage was utilized the anesthesiologist in charge made the determination regarding the use of irradiation prior to 2017, after which all salvaged blood was irradiated prior to transfusion. The device used to irradiate blood to prior to transfusion was an IBL 437C, a radioisotope irradiator – the dose or irradiation use was not specified. Ten patients (19.6%) developed tumor recurrence within a mean time frame of 2.45 years (SD 2.0 years). Tumor recurrence was significantly more frequent in patients with multifocal lesions (>3) in the explanted liver (p=0.017), but there was no difference between treatment groups in frequency of tumor recurrence (p=0.287): 4 (33%) patients without blood salvage, 2 (4.5%) patients with blood salvage without irradiation, and 4 (14.3%) patients with blood salvage with irradiation.

Poli et al. report on an uncontrolled prospective case series involving 15 patients undergoing radical retro-pubic prostatectomy with intraoperative autologous blood recovery at a Brazilian hospital between May 2006 and October 2006, testing whether irradiation eliminated viable tumor cells. (Reference 4) Researchers tested peripheral blood samples from patients for presence of hypermethylation as a surrogate of the presence of viable tumor cells collected at five timepoints during surgery and blood recovery: 1. whole blood during anesthetic induction, 2. recovered blood from the intraoperative field, 3. recovered blood after washing, 4. recovered blood after washing and leukocyte filtration, 5. Recovered blood after washing, filtration and irradiation. The irradiator used was a Gammacell 3000, a radioisotope irradiator. The recovered blood was not re-transfused. Mean age of the included patients was 61.3 years (range 41-75 years). The tumor-specific molecular marker was present in two patients in blood recovered from the intraoperative field, in three patients after washing, in two patients after washing and filtration, and in no patients after washing, filtration, and irradiation. It should be noted that there was inconsistency in the results as the patients who showed presence of tumor cells in blood samples collected during surgery were not the same as those that showed presence of tumor cells after washing or filtration.

Beck-Schimmer et al. describe an uncontrolled prospective case series involving 9 patients which explored potential immunological inflammatory responses to re-transfusion with

irradiated cell salvage blood by examining the presence of pro-inflammatory mediators in serum of nine patients undergoing gynecological cancer surgery (uterine and ovarian) at a hospital in Switzerland. (Reference 1) Intraoperatively salvaged blood was collected, washed, and irradiated with 50 Gy before being retransfused into patients. The irradiator used was not specified. Blood samples were collected from patients 30, 60, 120 minutes after retransfusion, and on the morning after surgery. Samples of cell salvaged blood were collected before irradiation, immediately after irradiation, and after 2 hours of storage at room temperature. In patients, a transient slight increase from baseline in leukocyte cell counts was noted 30, 60, and 120 minutes after re-transfusion but returned to baseline by 24 hours. No significant changes were found in qualitative cell counts of neutrophils, eosinophils, monocytes in patient serum. There did appear to be a difference between the cell salvaged blood and patient serum in the concentrations of the inflammatory mediators present, tumor necrosis factor-α, interleukin-1 β, or eotaxin. However, no significant change between the unirradiated or irradiated cell salvaged blood was found. The effect of irradiation on long term cell viability or function was not assessed.

Table 4. Outcomes of Included Observational Studies

Study details	Patients	Intervention(s)	Outcomes Assessed
Reference: Weller et al. (2021) (Reference 2) **Study design**: retrospective cohort study **Country**: Germany **Purpose**: provide data on recurrence of tumors or metastases in patients with hepatocellular carcinoma undergoing orthotopic liver transplant with intraoperative autotransfusion with irradiated blood **Conflict of interest**: none reported **Funding**: none reported **Irradiator Used:** IBL 437 C (radioisotope based) **Irradiation Dose:** Not Specified	**Number of patients**: 51 **Mean age, years (SD)**: 58 (6.5) **Age range, years**: Not Specified (NS) **Female, N (%)**: 11 (21.6) **Diagnosis**: hepatocellular carcinoma	**Intervention**: Intraoperative blood salvage (IOBS) with irradiation (n=28) **Comparator**: IOBS without irradiation (n=11), surgery without IOBS (n=12) **Follow-up period**: Not Specified (patients underwent surgery any time between 2002-2018) **Inclusion criteria**: age ≥18 years undergoing liver transplantation for hepatocellular carcinoma between 2002 and 2018 **Exclusion criteria**: Not Specified	**Primary outcome**: tumor recurrence 10/51 patients (p=0.287) • 4/12 patients (33%) without IOBS • 2/11 patients (4.5%) with IOBS without irradiation • 4/28 patients (14.3%) with IOBS with irradiation **Secondary outcome**: tumor recurrence among patients with multifocal lesions (>3 tumors on explanted liver), n=10 • 50% of patients with tumor recurrence had multifocal lesions • tumor recurrence was significantly (p=0.017) more common in patients with multifocal lesions, compared to those without • association of recurrence with treatment group for this subpopulation is not explored **Adverse events**: not reported **Other assessments:**

			Duration of OLT (mean±SD) • Without IOBS: 333.4±110.4 • IOBS without irradiation: 307.2±78.3 • IOBS with irradiation: 336.2±98.3 Retransfused blood (mL) (mean±SD) • Without IOBS: 0 • IOBS without irradiation: 1699±2423 • IOBS with irradiation: 869±605
Reference: Poli et al. (2008) (Reference 4) **Study design**: uncontrolled prospective case series **Country**: Brazil **Purpose**: demonstrate that viable tumor cells could be eliminated using leukodepletion filters followed by irradiation **Conflict of interest**: none reported **Funding**: none reported **Irradiator Used:** Gammacell 3000 (radioisotope based) **Irradiation Dose:** 25 Gy	**Number of patients**: 15 **Mean age, years (SD)**: 61.3 (9.3) **Age range, years**:41-75 **Female, N (%)**: 0 (0) **Diagnosis**: prostate cancer	**Intervention**: intraoperative blood recovery with washing, filtration, and irradiation at 25Gy. Blood was not re-transfused into patients. **Comparator**: none **Follow-up period**: none **Inclusion criteria**: patients with localized prostate cancer undergoing radical retro-pubic prostatectomy between May and October 2006, presence of GSTP-1 hypermethylation in the primary tumor **Exclusion criteria**: lack of GSTP-1 hypermethylation	**Primary outcome**: presence of hypermethylation of the pi-class glutathione-S transferase gene promoter as a marker of the presence of tumor cells N with blood sample positive for hypermethylation at different testing points: • intraoperative recovery: 2 • washed: 3 • washed and filtered: 2 • filtration and irradiation: 0 *note: Positive samples were not all from the same patients **Secondary outcome**: relation of aspirated blood volume and presence of hypermethylation: • positive 480±217 ml • negative 550±398 ml • p=0.70
Reference: Beck-Schimmer et al. (2004) (Reference 1) **Study design**: uncontrolled prospective case series **Country**: Switzerland **Purpose**: explore release of pro-inflammatory mediators in blood of patients receiving re-transfusion of irradiated	**Number of patients**: 9 **Mean age, years (SD)**: 63 (9) **Age range, years**: Not Specified **Female, N (%)**: 9 (100) **Diagnosis**: uterine or ovarian cancer	**Intervention**: intraoperative blood salvage with washing and irradiation at 50 Gy **Comparator**: none **Follow-up period**: 24 hours **Inclusion criteria**: patients undergoing major gynecological cancer surgery being	**Primary outcome**: presence of pro-inflammatory mediators at re-transfusion time points (*=significant difference from pre-transfusion at p<0.05 level) <u>leukocytes, 10^9L^{-1} (SD)</u> <u>in serum:</u> pre: 8.7 (3.2) 30 min post: 11.7 (3.8)* 60 min post: 11.7 (3.7)* 120 min post: 10.9 (3.1)*

intraoperative salvage blood **Conflict of interest**: none reported **Funding**: Schweizerische Gesellschaft für Anästhesiologie und Reanimation **Irradiator Used:** Not Specified **Irradiation Dose:** 50 Gy		treated with irradiated cell salvage **Exclusion criteria**: receipt of allogenic blood or blood products perioperatively	24 hours post: 9.7 (1.8) <u>neutrophils, % (SD)</u> in Serum pre: 84.2 (4.8) 30 min post: 84.9 (4.4) 60 min post: 86.4 (3.8) 120 min post: 86.3 (5.3) 24 hours post: 83.7 (4.4) <u>monocytes, % (SD)</u> in serum pre: 4.4 (2.0) 30 min post: 4.1 (2.3) 60 min post: 3.4 (1.5) 120 min post: 4.1 (1.5) 24 hours post: 6.0 (1.9) <u>eosinophils, % (SD)</u> in serum: pre: 0.67 (0.9) 30 min post: 0.5 (0.6) 60 min post: 0.5 (0.6) 120 min post: 0.5 (0.5) 24 hours post: 0.6 (0.3) <u>TNF-α, pg/mL, mean (SD)</u> in serum: Pre: 0 (1) 30 min post: 0 (0) 60 min post: 3 (8) 120 min post: 0 (0) 24 hours post: 2 (5) in CSB: Before irradiation: 23 (34) After irradiation: 25 (43) 2h post irradiation: 22 (39) <u>IL-1β, pg/mL, mean (SD)</u> in serum Pre: 0 (1) 30 min post: 0 (0) 60 min post: 3 (8) 120 min post: 0 (0) 24 hours post: 2 (5) in CSB: Before irradiation: 4 (7) After irradiation: 2 (4) 2h post irradiation: 3 (5) <u>eotaxin, pg/mL, mean (SD)</u> in serum pre: 3 (5)

			30 min post: 3 (7) 60 min post: 9 (11) 120 min post: 6 (9) 24 hours post: 10 (17) in CSB: Before irradiation: 12 (9) After irradiation: 15 (18) 2h post irradiation: 18 (18) <u>MCP-1, pg/mL, mean (SD)</u> in serum Pre: 541 (627) 30 min post: 527 (636) 60 min post: 643 (830) 120 min post: 503 (569) 24 hours post: 311 (146) in CSB: Before irradiation: 281 (212) After irradiation: 302 (211) 2h post irradiation: 350 (295)

Abbreviations: SD = standard deviation, , IL-1β=interleukin 1β, IOBS=intraoperative blood salvage, MCP1=monocyte chemoattractant protein-1, SD=standard deviation, TNF-α=tumor necrosis factor-α, CSB = cell-salvaged blood

Literature Reviews Summary

The sole systematic review located by Zaw et al., (Reference 5) included a reference to the Poli et al. article described above (Reference 4), but identified no new literature beyond those already captured in the systematic review.

Four narrative literature reviews were identified regarding interoperative blood salvage that included discussion of irradiation of salvage blood: Fischer et al 2019, Hansen et al 2002, Hansen et al. 2003, and Trudeau et al. 2012. Fischer et al. (Reference 6) offer a review of allogenic transfusion alternatives in oncological surgery, but references to intraoperative autologous transfusion of salvaged blood are primarily limited to studies involving no treatment to blood prior to reinfusion or leukocyte filtering alone. The paper includes a single paragraph that mentions irradiation of cell salvage blood to reduce risk of spread of cancer cells. No specific blood irradiators were identified. The authors cite the Hansen et al. 1999 (Reference 3) *in vitro* study as the sole source for justification for the use of 25–50 Gy irradiation.

As the Hansen et al. 1999 *in vitro* study (Reference 3), forms the basis of support for blood irradiation in all references located, it is summarized here. In the reference, lab-cultivated tumor cells as well as single cell suspensions of fresh samples of solid tumors were mixed with donor blood and subjected to 50 Gy in a blood irradiator (IBL 437C, a radioisotope irradiator), with actual measured dosing ranging from 43-52 Gy. Tumor cells were separated by centrifugation, viable tumor cell count was assessed, and colony-forming assay performed to assess proliferation capacity with BrdU staining used to assess DNA metabolism. No tumor cells irradiated with 50 Gy exhibited DNA metabolism after 10 days of cell culture, and no cell colonies were observed

indicating impaired proliferative ability. The study also investigated a variety of different tumor cell types for their radiosensitivity. As all the D_0 values (a measure of the relative radiosensitivity of the cell population) for the tumor cells were determined to be between 1-2.2 Gy, and assuming a worst case contamination of shed blood with 10^9 tumor cells, Hansen et al. calculated that 50 Gy would result in a 99.86% probability that no tumor cells would survive. Therefore, the concluded that intraoperatively salvaged blood could be safely returned to the patient – in that there would be minimal chance for tumor spread through retransfused blood – after irradiation with 50 Gy.

Trudeau et al. conducted a narrative review of articles published between 1973 and 2012 that included *in vitro* evidence related to removal of tumor cells from intraoperatively salvaged blood and clinical studies where this blood had been used in oncological patients. (Reference 7) They included studies that included leukocyte reduction filtration and/or gamma irradiation of salvaged blood, although the majority of the clinical studies located included neither method. The authors identify three articles exploring efficacy of gamma irradiation for removal of malignant cells from intraoperative salvage blood: the 2008 article by Poli et al. described above (Reference 4), the 1999 *in vitro* study by Hansen et al. described above (Reference 3), and a 2005 in vitro study by Futamura et al. (Reference 8) The latter two articles, as *in vitro* studies, did not meet inclusion criteria for the systematic review performed for this panel. There were no clinical studies identified in this review which examining tumor recurrence in patients who received intraoperatively salvaged blood after irradiation. The article does state their belief that the chief limitation of irradiation of intraoperatively salvaged blood is the availability of a gamma irradiator on site. It also notes the risks of moving autologous blood which is untested for transmissible diseases from the operating room to the transfusion medicine area, and the possible risk of wrong blood given to the wrong patient due to this movement.

A 2003 review of cell salvage in cancer surgery was authored by Hansen, whose 1999 paper is generally cited as the scientific basis for irradiation of intraoperatively salvaged blood to prevent metastasis. (Reference 9) The review discusses the limitations of determining safety and efficacy of cell salvage for oncology patients in clinical studies, and identifies *in vitro* studies examining tumor cells in blood shed during oncological surgery as the only method with sufficiently high sensitivity and specificity for properly assessing safety and efficacy of intraoperative blood salvage in oncology surgery. Blood irradiation is identified as the solution, citing his 1999 study. (Reference 3) The purpose of Hansen's review is to provide support for his claim that blood irradiation is an efficacious, practical, and safe method to eliminate contaminating tumor cells, rather than providing a full exploration of the body of evidence and synthesis of results.

In a 2002 article, Hansen et al. purport to offer support for the safety and efficacy of intraoperative blood salvage in cancer patients based on their own experience with more than 700 patients at a medical center in Regensburg, Germany (Reference 10). The authors cite much of the same information present in the 2003 review discussed above, and describe their *in vitro* studies to support the safety and efficacy of irradiation. Their use of intraoperative blood salvage with irradiation in oncology surgery is repeatedly cited, but no data is provided beyond a table documenting blood loss and salvaged blood in surgeries at their institution related to different tumor types. Support for efficacy and safety of blood salvage with blood irradiation in cancer surgery comes from a 1997 book chapter authored by Hansen, (Reference 11) a 1999 article in

German authored by Hansen et al. (Reference 12) the widely cited 1999 article by Hansen et al. (Reference 3) and a 1999 article by the Italian team of Valbonesi et al. (Reference 13) which describes their own personal experience using gamma and X-ray irradiation of salvaged blood from cancer patients in an Italian hospital and provides outcomes of *in vitro* studies.

Professional Guidelines Summaries

Three professional guidelines were identified from Germany, Italy, and Spain. When irradiation of intraoperative salvaged blood in cancer surgery is referenced, professional guidelines rate the strength of evidence as weak -with uncertainty in the risk to benefit balance and that other alternatives may be equally reasonable. In 2014 guidelines from the German Medical Association related to autologous transfusion, intraoperative cell salvage is strongly recommended for cancer patients on the condition that salvaged blood is irradiated at 50 Gy prior to re-transfusion. (Reference 14) The level of evidence is graded 2C+, indicating that no randomized, controlled studies were found but data can be extrapolated from other studies. The sole reference for this recommendation is a 1999 article by Hansen et al. (Reference 12) that references the 1999 Transfusion publication (Reference 3). In 2011 guidelines, the Italian Society of Transfusion Medicine and Immunohaematology Working Party suggests that intraoperative blood salvage be used in cancer surgery provided that leukodepletion filters are used and blood is irradiated at 25 Gy prior to re-transfusion. (Reference 15) Strength of evidence is rated as weak, with a grade of 2C. A Spanish consensus statement regarding alternatives to allogeneic blood transfusion published in 2013 suggests use of intraoperative cell salvage during surgical resection of hepatic or urological cancers when accompanied by filtration and/or irradiation of salvaged blood, with a grade of 2C. (Reference 16) No recommended irradiation dosage is specified.

Appendix D: References from Literature Review

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