Managing the Patient With Multiple Primary Tumors

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Abstract

Multiple primaries are defined as more than one synchronous or metachronous cancer in the same individual. They can pose challenges to clinicians, as the goal is to find an anticancer therapy strategy that covers both cancer types without increased toxicity or drug interactions, and does not negatively impact a patient's overall outcome. At JADPRO Live 2022, presenters tackled this complicated topic by reviewing diagnostic criteria, epidemiology, and risk factors, demonstrating the prioritization of treatment, and discussing the role of the advanced practitioner in collaborative, interdisciplinary management of the patient with multiple primary tumors.

As the incidence of patients presenting with multiple primary tumors continues to rise, it is crucial for health-care providers to have a comprehensive understanding of the unique challenges and management strategies involved in caring for this complex patient population.

During JADPRO Live 2022, Holly Chitwood, DNP, APRN, FNP, AGACNP, and Tamara Carey, MSN, APRN, FNP, of Markey Cancer Center, University of Kentucky, described diagnostic criteria for multiple primary tumors and examined the incidence and risk factors associated with this condition. They also prioritized treatment options with respect to risk of mortality, progression of disease, and the expected toxicity of therapies (Table 1).

MULTIPLE PRIMARY SOLID TUMORS: EPIDEMIOLOGY

Multiple primary tumors refer to the simultaneous occurrence of two or more primary tumors in a single individual at different anatomic sites or histological types. The Surveillance, Epidemiology, and End Results (SEER) program is commonly used to differentiate between secondary tumors, primary tumors, and multiple primary tumors (Adamo et al., 2022). Synchronous tumors are defined as occurring within 6 months of a primary index tumor, while metachronous tumors occur more than 6 months after the primary index tumor.

According to Dr. Chitwood, the management of multiple primary hematologic malignancies is particularly complicated and requires a specific

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calculator from the SEER program to determine if they are separate hematologic malignancies.

"A combination of hematologic malignancies with a solid tumor malignancy is rare, but it does occur," said Dr. Chitwood. "The incidence of multiple primary tumors varies in the literature, but it is estimated to be between 2% and 17%." (Weir et al., 2013)

The National Institutes of Health reports an increased incidence of multiple primary tumors with some cancers, including urinary bladder, oral cavity, head and neck, and melanoma. It is worth noting, however, that lung and bronchus cancer is not high on the list, said Dr. Chitwood.

RISK FACTORS

The National Comprehensive Cancer Network (NCCN) Guidelines recognize multiple risk factors for the development of multiple primary tumors, which include:

1. Inherited cancer syndromes: Certain inherited genetic conditions such as Lynch syndrome, familial adenomatous polyposis, and von Hippel-Lindau disease, are associated with an increased risk of developing multiple types of cancer throughout a patient's lifetime.
2. Lifestyle factors: Risk factors such as obesity and lack of physical activity have been linked to an increased risk of developing certain types of cancer, such as breast and ovarian cancer.
3. Hormonal factors: Hormonal agents such as hormone replacement therapy are associated with an increased risk of ovarian cancer, while long-term use of oral contraceptives have been linked to cervical and breast cancer.
4. Previous cancer therapy: Certain cancer treatments such as radiation therapy and chemotherapy can increase the the risk of developing secondary malignancies later.
5. Environmental and occupational exposures: Exposure to certain toxins such as asbestos and certain chemicals can increase the risk of developing certain types of cancer, such as mesothelioma.
6. Increased cancer survival: With the advancement of cancer treatment and increasing survival rates, patients have more chances to develop other cancers, which are detected through ongoing surveillance imaging.
7. Prolonged immunosuppression: Patients with weakened immune systems, such as those who have received organ transplants, are at increased risk of developing certain types of cancer, such as skin, lung, and head and neck cancers.

Table 1. Epidemiology of Multiple Primary Tumors

First primary cancer site (index site)	Subsequent primary
Brain/CNS	2%
Breast	10%
Cervix uteri	7%
Colorectal	10%
Corpus/uterus	11%
Esophagus	3%
Renal pelvis/kidney	10%
Leukemia	6%
Liver	1%
Lung/bronchus	4%
Melanoma	10%
Myeloma	5%
NHL	7%
Oral cavity/pharynx	15%
Ovary	5%
Prostate	9%
Thyroid	7%
Urinary bladder	16%

Note. The occurrence of multiple primary tumors is estimated between 2% and 17%. CNS = central nervous system; NHL = non-Hodgkin lymphoma. Information from Copur & Manapuram (2019); Hayat et al. (2007); Vogt et al. (2017); Weir et al. (2013).

When evaluating patients with multiple primary tumors, the NCCN Guidelines recommend high-quality imaging for anatomical evaluation of the tumors, tissue biopsy to determine the type of cancer, molecular analysis of the tumor for personalized treatment, and genetic testing for patients diagnosed before age 50, patients with pancreatic cancer, or those with multiple malignancies.

"Genetic testing has become a critical part of cancer treatment, particularly for patients with

multiple primary tumors," said Mrs. Carey, who noted, for example, that DNA mismatch repair in genes *MSH2*, *MSH6*, *MLH1*, and *PMS2* are diagnostic for Lynch syndrome. "Additionally, the NCCN Guidelines recommend tumor-board discussion as an important step for collaborative decision-making on the correct sequence of treatments, referrals, and additional workup."

BIOMARKERS AND THEIR ROLE IN PRECISION MEDICINE

Biomarkers are molecules or genetic changes that can be measured in a patient's blood, tissue or other bodily fluids and can provide important information about a patient's cancer. They can be used for prognosis, diagnosis, and treatment selection, as well as for monitoring response and recurrence.

Prognostic biomarkers can provide information on overall prognosis, such as high risk, favorable risk, or good risk. Diagnostic biomarkers, such as those used in immunohistochemistry, can be used to help determine the type of cancer present. Predictive biomarkers, on the other hand, can be used to identify which drugs will be most effective in treating a specific cancer.

Monitoring biomarkers, also known as tumor markers, can be used to track response to treatment and detect recurrence. These include biomarkers such as carcinoembryonic antigen and CA 19-9.

Circulating tumor DNA is a rapidly developing field in oncology. It is the DNA that circulates in the bloodstream and is derived from a patient's tumor. The technology is still evolving, but it has the potential to provide early detection of molecular residual disease and inform treatment decisions. Circulating tumor DNA can be used to identify the presence of tumor-specific mutations, which can be used to monitor the progression of the disease and to identify patients who may benefit from targeted therapy.

According to Dr. Chitwood, however, the use of circulating tumor DNA is controversial, and its clinical utility is still under evaluation.

TREATMENT OPTIONS AND INTERDISCIPLINARY CARE

Dr. Chitwood also underscored the need for an interdisciplinary approach when managing patients with multiple primary tumors, with clear communication and collaboration among providers to determine surveillance and treatment priorities.

"Everybody can't be the leader," she emphasized. "You must have a collaborative plan of care, and it must be interdisciplinary."

Each primary tumor should be evaluated individually, and the treatment plan should be tailored to the specific characteristics of each cancer, she added. Chemotherapy, targeted therapy, and immunotherapy are among the treatment options available.

"When managing multiple primary tumors, it is important to consider whether there is a drug or therapy that can provide a two-in-one benefit for treating both cancers," said Dr. Chitwood. "This should be evaluated in light of potential toxicities."

Prioritizing treatment should also consider the biology of the cancer, including its spread and potential for metastasis. Factors such as the stage of the cancer, the presence of lymph node involvement, and the aggressiveness of the cancer should also be considered.

"Ultimately, treatment decisions should prioritize life-threatening conditions," said Dr. Chitwood. "In cases where a patient presents through the emergency room with an acute issue such as obstruction of an airway or a ureter, or a cardiac problem, for example, these take priority over other considerations."

However, it's also important to consider the severity of the patient's discomfort, as well as the toxicity of treatment in relation to the patient's age and comorbidities, Dr. Chitwood noted. This may play a role in determining which cancer to treat first.

"When managing multiple primary tumors, it is important to consider all possible treatment options. It is important to be clear with patients that multiple primary tumors may not be curative, but are rather palliative, with the aim of halting the progression of disease and maintaining the best quality of life without harmful effects of cancer," said Dr. Chitwood. "It is also important to establish goals of care, be open when there is no clinical benefit, and discuss hospice where appropriate. Patients may have the option to be more aggressive with treatment, but it is important to consider their preferences and goals of care in the treatment plan."

According to Dr. Chitwood, it is also important to conduct thorough biopsies and molecular analysis, including the use of circulating tumor DNA, and to involve interdisciplinary specialist services to determine the best course of treatment.

"Immune checkpoint inhibitors and immunotherapy may be especially useful for patients with certain genetic syndromes, such as Lynch syndrome," she concluded. "However, it is important to keep in mind the potential adverse events associated with these therapies and to consider the patient's comorbidities when determining the treatment plan." ●

Disclosure

The presenters have no relevant financial relationships to disclose.

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