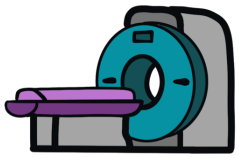
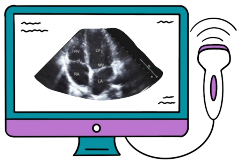
Society for Maternal-Fetal Medicine

Consult Series #76

CANCER IN PREGNANCY

EVALUATION AND DIAGNOSIS OF SUSPECTED CANCER





We suggest that ultrasonography and non-contrast MRI be used as first-line imaging techniques in the evaluation of a pregnant person with suspected cancer

Although noncontrast MRI and ultrasonography are first-line diagnostic imaging modalities in pregnancy, we recommend that CT with or without contrast, gadolinium contrast for MRI, and 18-FDG-PET/CT not be withheld from a pregnant person if clinically indicated

Lactating patients exposed to iodinated contrast or gadolinium should not interrupt their breastfeeding

TABLE 1 Approximate fetal dose from common diagnostic imaging techniques [35, 41–46].

Conventional radiography	Mean (mGy[a])	Maximum (mGy)
Abdomen	1.4	4.2
Chest	<0.01	<0.01
Lumbar spine	1.7	10
Pelvis	1.1	4
Skull	<0.01	<0.01
Thoracic spine	<0.01	<0.01
Mammography	Negligible	Negligible
Computed tomography	**Mean (mGy)**	**Maximum (mGy)**
Abdomen/pelvis	10	50[b]
Chest	0.06	0.96
Head	<0.005	0.05
Lumbar spine	2.4	8.6
Nuclear medicine	**Range (mGy)**	
Sentinel node mapping	<0.05-2.2	
Bone scintigraphy	2-3.3	
FDG-PET	1.1-50	

TABLE 2 Adverse effects on offspring of radiation during pregnancy [29, 34].

Gestational age at exposure	Effects	Estimated threshold dose
0–2 weeks	Pregnancy loss (all or none)	50–100 mGy[a]
2–8 weeks	Congenital malformations (skeleton, eyes, genitalia) Fetal growth restriction	200 mGy 200–250 mGy
8–15 weeks	Severe intellectual disability (high risk) Intellectual deficit Microcephaly	60–310 mGy 25 IQ-point loss per 1000 mGy 200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy

[a]1 Gy = 1000 mGy = 100 rad.

TABLE 3 Fetal risks based on radiation dose and gestational age [36].

Gestational age at exposure	Radiation dose <50 mGy[a] (<5 rad)	50–100 mGy (5–10 rad)	>100 mGy (>10 rad)
0–2 weeks	None	None	None
3–4 weeks	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Possible early pregnancy loss
5–10 weeks	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Possible malformations increasing in likelihood as dose increases
11–17 weeks	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Increased risk of deficits in IQ or intellectual disability that increase in frequency and severity with increasing dose
18–27 weeks	None	None	IQ deficits not detectable at diagnostic doses
>27 weeks	None	None	Not applicable to diagnostic medicine

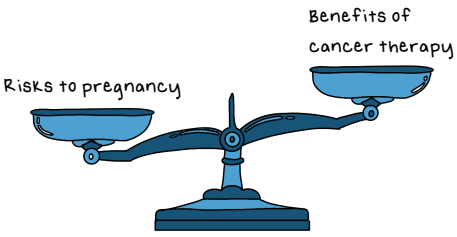
Note: Adapted from [36].
[a]1 Gy = 1000 mGy = 100 rad.

THERAPEUTIC PRINCIPLES

Thromboprophylaxis

We recommend initiating thromboprophylaxis for all patients with active hematological or gynecological cancers during pregnancy and considering thromboprophylaxis for all patients with non-hematological or non-gynecological cancers during pregnancy, based on individual risk factors

Surgery



We recommend that surgery for the treatment of cancer should not be delayed or withheld from a pregnant patient at any gestational age in pregnancy

- General anesthesia does not increase the risk of fetal malformations

Chemotherapy, targeted therapy, or immunotherapy

We recommend that chemotherapy generally be administered after 12 weeks of gestation, provided that the patient desires to continue the pregnancy and that delaying treatment until after 12 weeks of gestation is not expected to significantly change the pregnant patient's prognosis compared to initiating treatment immediately after diagnosis

- Chemotherapy has been associated with spontaneous preterm birth and fetal growth restriction (see table 4)
- After 34 weeks of gestation, most chemotherapy agents are discontinued to allow for maternal and fetal bone marrow recovery before delivery

Radiation therapy

Usually postponed until postpartum

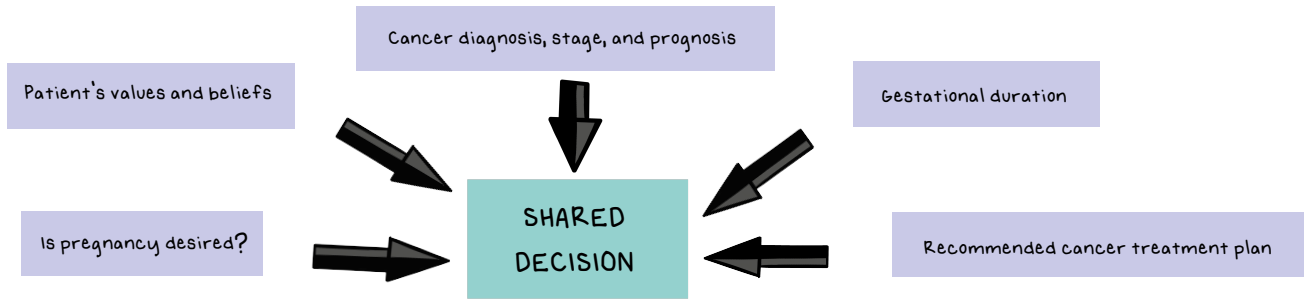
TABLE 4 Recommendations on the use of chemotherapy, targeted therapy, and immunotherapy agents in pregnancy [5, 15, 24, 25, 49, 63–73].

Agent	Mechanism of action	Notable side effects/toxicities[a]	Use in pregnancy, by trimester		
			First	Second	Third
Alkylating agents					
Cyclophosphamide	DNA alkylation	Hemorrhagic cystitis	Avoid[b]	Possible	Possible
Anthracyclines					
Doxorubicin	DNA intercalation, topoisomerase inhibitor	Cardiotoxicity for the patient, rare reports of cardiotoxicity in neonates	Avoid[b]	Possible	Possible
Daunorubicin	DNA intercalation, topoisomerase inhibitor	Cardiotoxicity for the patient, rare reports of cardiotoxicity in neonates	Avoid[b]	Possible	Possible
Epirubicin	DNA intercalation, topoisomerasone inhibitor	Cardiotoxicity for the patient, rare reports of cardiotoxicity in neonates	Avoid[b]	Possible	Possible
Idarubicin	DNA intercalation, topoisomerase inhibitor	Transient neonatal cardiomyopathy	Avoid	Avoid	Avoid
Taxanes					
Paclitaxel	Microtubule stabilization	Peripheral neuropathy, acral erythema	Avoid	Possible	Possible
Docetaxel	Microtubule stabilization	Peripheral neuropathy, acral erythema	Avoid	Possible	Possible
Platinum agents					
Carboplatin	Covalent binding with DNA	Nephrotoxicity Maternal and neonatal ototoxicity, but less than cisplatin	Avoid	Possible	Possible
Cisplatin	Covalent binding with DNA	Maternal and neonatal ototoxicity	Avoid	Possible	Possible
Oxaliplatin	Covalent binding with DNA	No reports of ototoxicity in adults	Avoid	Possible	Possible
Antimetabolites					
5-fluorouracil	Thymidylate synthase inhibitor	Diarrhea	Avoid	Possible	Possible
6-mercaptopurine	DNA synthesis inhibitor	Hepatotoxicity	Avoid[b]	Possible	Possible
Methotrexate	Dihydrofolate reductase inhibitor	Hepatotoxicity	Avoid[b]	Possible[c]	Possible
Cytarabine	DNA replication inhibitor	Corneal toxicity	Avoid	Possible	Possible
Vinca alkaloid					
Vincristine	Microtubule formation inhibitor	Neurotoxicity	Possible[d]	Possible	Possible
Vinblastine	Microtubule formation inhibitor	Neurotoxicity	Possible[d]	Possible	Possible
Bleomycin	DNA oxidative damage	Pulmonary toxicity	Avoid	Possible	Possible
Targeted therapy and immunotherapy					
Trastuzumab	Human epidermal growth factor receptor-2/neu receptor	Cardiotoxicity Fetal oligohydramnios and neonatal renal failure	Avoid	Avoid	Avoid
Rituximab	CD20 on B cells	Transient absence of neonatal B cells	Possible	Possible	Possible
Nivolumab	PD-1 receptor on T cells	Immune-related adverse events, hypersensitivity	Possible[d]	Possible[d]	Possible until 32 weeks[d]
Ipilimumab	CTLA-4 on T cells	Immune-related adverse events	Possible[d]	Possible[d]	Possible until 32 weeks[d]
Tamoxifen	Selective estrogen receptor modulator	Venous thromboembolism Fetal skeletal abnormalities, uterine epithelial dysplasia, ambiguous genitalia	Avoid	Avoid	Avoid
Imatinib	Tyrosine kinase inhibitor	Fetal exencephaly, encephalocele, calvarial hypoplasia in first-trimester exposure only	Avoid	Possible	Possible
Nilotinib	Tyrosine kinase inhibitor		Avoid	Possible[d]	Possible[d]
Dasatinib	Tyrosine kinase inhibitor	Cardiotoxicity Fetal leukopenia, thrombocytopenia	Avoid	Avoid	Avoid
Vemurafenib	*BRAF* inhibitor	Skin toxicity (toxic epidermal necrolysis), hepatotoxicity	Avoid	Possible[d,e]	Possible[d,e]

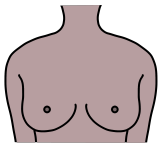
[a] Maternal toxicities listed unless otherwise specified for fetus or newborn.
[b] Consider for use as induction therapy in patients with acute leukemia.
[c] Avoid intrathecal methotrexate use before 20 weeks of gestation.
[d] Based on limited data.
[e] Caution in patients with sulfa allergy.

MANAGEMENT

Management considerations when cancer is diagnosed during pregnancy



Breast

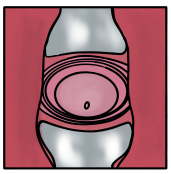


Ultrasound is recommended as the first-line imaging for breast masses detected in pregnancy, followed by mammography once cancer is diagnosed

Surgical treatment can be performed in any trimester

Chemotherapy in the second and third trimesters are based on tumor biology and prognostic factors and can be given in neoadjuvant or adjuvant settings

Cervical



Diagnostic conization for suspected cancer should be performed up to 22 weeks

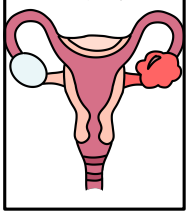
Simple trachelectomy for IB1 should be performed in highly selected cases

Lymph node staging should be performed if technically feasible until 24 weeks

Sentinel lymph node biopsy should be performed with isocyanine green dye

For advanced disease, neoadjuvant platinum-based chemotherapy during the second and third trimesters should be given

Ovarian

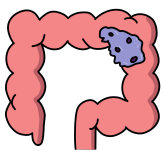


Surgical management for staging in the setting of a suspicious mass via laparoscopy is preferred

If bilateral salpingo-oophorectomy prior to 12 weeks of gestation, progesterone supplementation can be considered

Ovarian cancer in the second dand third trimesters is most commonly treated with platinum-based chemotherapy

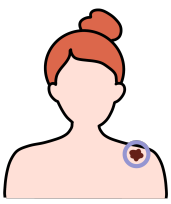
Colorectal



When clinically indicated, endoscopy should be performed at any gestational age

Pregnant patients should receive the same regimens as nonpregnant patients for the treatment of colorectal cancer

Melanoma



For suspicious skin lesions, wide local incision with or without sentinel lymph node biopsy can be performed at any gestational age

Immunotherapy agents should be used with caution and after thorough counseling on the risks and benefits for pregnant patients with metastatic melanoma

Non-Hodgkin lymphoma

Consider diagnosis in patients who present with bilateral breast or ovarian masses during pregnancy

Masses should not be surgically removed after biopsy confirming non-Hodgkin disease, as they typically respond to systemic therapy

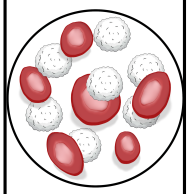
Prognosis is comparable to prognosis of nonpregnant patients

Hodgkin lymphoma

Prognosis is comparable to prognosis of nonpregnant patients

Treatment includes chemotherapy with or without radiation

Acute leukemia



Often diagnosed after abnormal routine prenatal laboratory studies showing leukocytosis, anemia, thrombocytopenia, or when a patient presentswith bruising or mucosal bleeding

Administration of chemotherapy must not be delayed

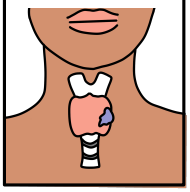
When indicated, leukopheresis can be performed at any gestational age

Induction chemotherapy may be considered to facilitate safe abortion care (when chosen)

Chronic leukemia

In patients who are asymptomatic and without splenomegaly, observation without treatment can be considered

Thyroid



Thyromegaly is a common physical exam finding during pregnancy and does not require specific follow-up

Prominent nodules should be further investigated

Surgery is the mainsstay of treatment and can be performed at any gestational age when indicated by cancer subtype or lymph node status

Radioactive iodine I-131 is contraindicated during pregnancy

Thyroid supplementation is initiated after total thyroidectomy, and if performed before or during pregnancy, monitoring of serum calcium levels should be considered in the event of unintentional parathyroid tissue excision

How should patients be counseled regarding fetal exposure to chemotherapy, targeted therapy, and immunotherapy in pregnancy?

Before beginning chemoterhapy during preganncy, the patient should be counseled regarding fetal risks, including congenital malformations with first-trimester exposure, fetal growth abnormalities, potential immunosuppression, and long-term developmental outcomes

To improve long-term neurodevelopmental outcomes of children exposed to chemotherapy in uteri, we suggest avoiding clinician-initiated preterm delivery when possible

Supportive medications for chemotherapy side effects during pregnancy

We recommend intravenous methyldprednisolone, 62.5 mg (corresponding to 10 mg of dexamethasone), or oral prednisolone, 30 mg (corresponding to 6 mg of dexamethasone), as first-line therapy for chemotherapy-induced nausea when corticosteroids are indicated

What type of fetal ultrasound surveillance is indicated in patients with cancer during pregnancy?

Detailed fetal anatomy survey

We recommend serial fetal growth surveillance every 3-4 weeks in pregnancies with an active cancer diagnosis, regardless of treatment

We recommend initiation of antenatal fetal surveillance starting at 32 weeks of gestation in pregnancies with an active cancer diagnosis, regardless of treatment, unless indicated earlier for maternal or fetal reasons

How does a cancer diagnosis during pregnancy guide the timing and mode of delivery?

We recommend that planned delivery prior to 37 weeks of gestation in pregnant patients with cancer generally be avoided unless indicated for medical or obstetrical reasons

We recommend that chemotherapy treatment generally be stopped by 34 weeks of gestation to allow 3-4 weeks for recovery of myelosuppression before spontaneous labor or planned delivery, except for weekly paclitaxel, which can be administered up to 35 or 36 weeks, as only 1-2 weeks are necessary for recovery before delivery

We recommend that the mode of delivery be determined by routine obstetrical indications for most patients with cancer in pregnancy

We recommend a placental pathology examination in all cases of cancer during pregnancy, regardless of cancer type or treatment

How should a patient with cancer be managed in the postpartum period?

Prophylactic anticoagulation, particularly in the setting of additional risk factors, should be considered during the postpartum period

How does prenatal aneuploidy screening with cfDNA affect the detection of occult malignancies?

We recommend that cancer be considered as part of the differential diagnosis for pregnant patients with multiple chromosomal aneuploidies or single autosomal monosomy detected by cfDNA screening that is discordant with fetal findings

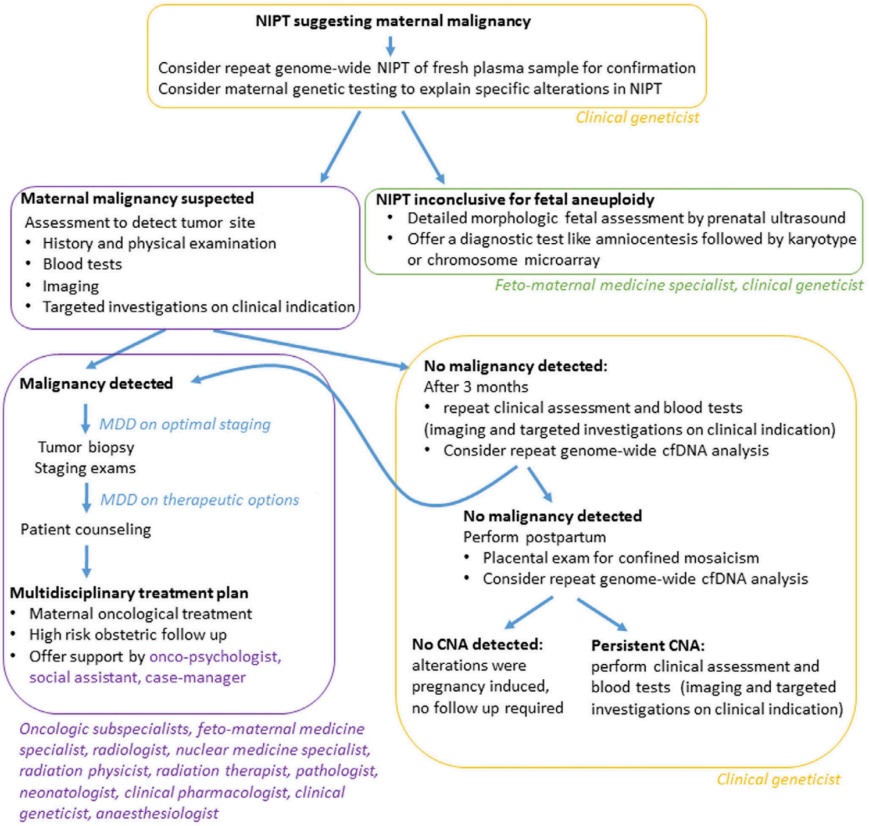


FIGURE 2 Diagnostic workup when noninvasive prenatal testing suggests maternal cancer [253]. cfDNA, cell-free DNA; CNA, copy number alterations; MDD, multidisciplinary discussion; NIPT, noninvasive prenatal testing. Note that the terminology "prenatal screening with cell-free DNA (cfDNA)" is preferred over "noninvasive prenatal testing (NIPT)." Reprinted with permission from [253].