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MEDICAL POLICY – 8.01.11

Transcatheter Arterial Chemoembolization (TACE) to Treat Primary or Metastatic Liver Malignancies

BCBSA Ref. Policy:	8.01.11
Effective Date:	Oct. 1, 2024
Last Revised:	Sept. 23, 2024
Replaces:	8.01.505

RELATED MEDICAL POLICIES:

7.01.95	Radiofrequency Ablation of Miscellaneous Solid Tumors Excluding Liver Tumors
7.01.133	Microwave Tumor Ablation
8.01.521	Radioembolization for Primary and Metastatic Tumors of the Liver

Select a hyperlink below to be directed to that section.

Clicking this icon returns you to the hyperlinks menu above.

Introduction

Embolization is a procedure to block blood flow. When the material used to block the blood flow contains chemotherapy agents as well, it is a way to treat liver cancer in some situations. This treatment is usually known as Transcatheter Arterial Chemoembolization (TACE). In this procedure a catheter (a long, thin, hollow tube) is inserted in an artery near the groin. It's threaded to the tumor's blood supply. Chemotherapy and tiny particles are then sent directly into the tumor. The particles block off — embolize — the artery feeding the tumor, causing it to shrink. The chemotherapy works to kill the cancer cells. This treatment can be used in the liver because it has two sources of blood: the portal vein and the hepatic artery. The portal vein supplies most of the blood to the liver. The hepatic artery supplies a lesser amount, and tumors that grow in the liver usually get their blood supply from the hepatic artery. As a result, TACE can be used to starve the blood supply of the tumor usually without affecting the blood supply to the rest of the liver. This policy describes when TACE may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Treatment	Medical Necessity

Transcatheter hepatic arterial chemoembolization	**Transcatheter hepatic arterial chemoembolization may be considered medically necessary in the following conditions:**
	• Hepatocellular cancer that is unresectable but confined to the liver and not associated with portal vein thrombosis and liver function is not characterized as Child-Pugh class C*
	• As a bridge to transplant in individuals with hepatocellular cancer where the intent is to prevent further tumor growth and to maintain an individual's candidacy for liver transplant, and the following is present:
	  ○ A single tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size
	  ○ Absence of extrahepatic disease or vascular invasion
	  ○ Child-Pugh class A or B*
	• Treat liver metastasis in symptomatic individuals with metastatic neuroendocrine tumor with both of the following:
	  ○ Symptoms persist despite systemic therapy
	AND
	  ○ Individuals are not candidates for surgical resection
	• To treat liver metastasis in individuals with liver-dominant metastatic uveal melanoma
	
	Note: *See **Related Information** for Child-Pugh Classification

Treatment	Investigational
Transcatheter hepatic arterial chemoembolization	**Transcatheter hepatic arterial chemoembolization is considered investigational in the following conditions:** • As neoadjuvant or adjuvant therapy in hepatocellular cancer that is considered resectable • When used in combination with radiofrequency ablation (RFA) to treat resectable or unresectable hepatocellular carcinoma

Treatment	Investigational
	• To treat unresectable cholangiocarcinoma • To treat liver metastases from any other tumors or to treat hepatocellular cancer that does not meet the criteria noted above, including recurrent hepatocellular carcinoma • To treat hepatocellular tumors prior to liver transplantation except as noted above

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the relevant history and physical of ANY these situations:
  - The individual has primary liver cancer that cannot be surgically removed, located only in the liver and does not involve clot or narrowing of the portal vein
  - As a short-term treatment for an individual with primary liver cancer waiting for a liver transplant, and the following are true
    - A single tumor less than 5 cm or no more than 3 tumors each less than 3 cm in size
    - Absence of extrahepatic disease or vascular invasion
    - Child-Pugh class A or B
  - The individual has tumors from neuroendocrine cancer that have spread to the liver when the tumors can't be removed surgically and have not responded to other therapy
  - The individual has tumors in the liver that have spread from liver-dominant metastatic uveal melanoma

Coding

Code	Description
CPT	
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Child-Pugh Classification of Liver Disease

Parameter	Points assigned		
	1	2	3
Ascites	None	Suppressed with meds	Refractory
Bilirubin	< 34 µM	34 - 50 µM	>50 µM
Albumin	> 35 g/L	28 – 35 g/L	< 28 g/L
INR	< 1.7	1.7 – 2.2	> 2.2
Encephalopathy	Grade 0	Grade 1 – 2 or suppressed with meds	Grade 3 – 4 or refractory
-Grade 0: normal cognition -Grade 1: euphoria, fluctuation in level of consciousness, slurred/disoriented speech -Grade 2: drowsiness, inappropriate behavior, loss of sphincteric control -Grade 3: marked confusion, stupor, incoherent speech -Grade 4: coma			
Class A	5 – 6 points	"well-compensated"	
Class B	7 – 9 points	"significant functional impairment"	
Class C	10 – 15 points	"decompensated liver function"	

Source: http://www.bccancer.bc.ca/books/PublishingImages/Gastrointestinal/Child-Turcotte-Pugh.PNG Accessed August 16, 2024.

Evidence Review

Description

Transcatheter arterial chemoembolization (TACE) of the liver is a proposed alternative to conventional systemic or intra-arterial chemotherapy and to various nonsurgical ablative techniques, to treat resectable and nonresectable tumors. TACE combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia secondary to the embolization raises the drug concentration compared with infusion alone, extending the

retention of the chemotherapeutic agent and decreasing systemic toxicity. The liver is especially amenable to such an approach, given its distinct lobular anatomy, the existence of two independent blood supplies, and the ability of healthy hepatic tissue to grow and thus compensate for tissue mass lost during chemoembolization.

Background

Transcatheter Arterial Chemoembolization

Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure performed by interventional radiologists who inject highly concentrated doses of chemotherapeutic agents into the tumor tissues and embolic agent(s) to restrict tumor blood supply. The embolic agent(s) causes ischemia and necrosis of the tumor and slows anticancer drug washout. The most common anticancer drugs used in published TACE studies for hepatocellular carcinoma (HCC) include doxorubicin (36%), followed by cisplatin (31%), epirubicin (12%), mitoxantrone (8%), and mitomycin C (8%).[1]

The TACE procedure requires hospitalization for placement of a hepatic artery catheter and workup to establish eligibility for chemoembolization. Before the procedure, the patency of the portal vein must be demonstrated to ensure an adequate posttreatment hepatic blood supply. With the individual under local anesthesia and mild sedation, a superselective catheter is inserted via the femoral artery and threaded into the hepatic artery. Angiography is then performed to delineate the hepatic vasculature, followed by injection of the embolic chemotherapy mixture. Embolic material varies but may include a viscous collagen agent, polyvinyl alcohol particles, or ethiodized oil. Typically, only one lobe of the liver is treated during a single session, with subsequent embolization procedures scheduled five days to six weeks later. In addition, because the embolized vessel recanalizes, chemoembolization can be repeated as many times as necessary.

Adverse Events

TACE of the liver has been associated with potentially life-threatening toxicities and complications, including severe postembolization syndrome, hepatic insufficiency, abscess, or infarction. TACE has been investigated to treat resectable, unresectable, and recurrent hepatocellular carcinoma, cholangiocarcinoma, liver metastases, and in the liver transplant setting. Treatment alternatives include resection when possible, other locally ablative techniques (e.g., radiofrequency ablation, cryoablation) and chemotherapy administered systemically or by

hepatic artery infusion. Hepatic artery infusion involves the continuous infusion of chemotherapy with an implanted pump, while TACE is administered episodically. Hepatic artery infusion does not involve the use of embolic material.

Summary of Evidence

Unresectable and Resectable Hepatocellular Carcinoma

For individuals who have unresectable hepatocellular carcinoma (HCC) confined to the liver and not associated with portal vein thrombosis who receive TACE, the evidence includes several randomized controlled trials (RCTs), large observational studies, and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Evidence from one RCT has suggested that survival with TACE is at least as good as with systemic chemotherapy. One systematic review has highlighted possible biases associated with RCTs that compared TACE with no therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have resectable HCC who receive neoadjuvant or adjuvant TACE, the evidence includes several RCTs and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Studies have shown little to no difference in overall survival rates with neoadjuvant TACE compared with surgery alone. A meta-analysis found no significant improvements in survival or recurrence with preoperative TACE for resectable HCC. While both RCTs and the meta-analyses that evaluated TACE as adjuvant therapy to hepatic resection in HCC reported positive results, the quality of individual studies and the methodologic issues related to the meta-analyses preclude certainty when interpreting the results. Well-conducted multicentric trials from the US or Europe representing relevant populations with adequate randomization procedures, blinded assessments, centralized oversight and publication in peer-reviewed journals are required. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have resectable HCC who receive TACE plus radiofrequency ablation (RFA), the evidence includes a single RCT and a systematic review. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCT failed to show the superiority in survival benefit with combination TACE plus RFA treatment compared with surgery for HCC lesions 3 cm or smaller. Further, an ad hoc subgroup analysis showed a significant benefit for surgery in recurrence and overall survival in individuals with lesions larger than 3 cm. It cannot be determined from this trial whether TACE plus RFA is

as effective as surgical resection for these small tumors. The systematic review, which included mostly retrospective observational studies, did not find a survival benefit with TACE plus RFA over surgery alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable HCC who receive TACE plus RFA, the evidence includes multiple systematic reviews and RCTs. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple meta-analyses and RCTs have shown a consistent benefit in survival and recurrence-free survival favoring combination TACE plus RFA over RFA alone. However, results of these meta-analyses are difficult to interpret because the pooled data included heterogeneous individual populations and, in a few cases, data from a study retracted due to questions about data veracity. A larger well-conducted RCT has reported a relative reduction in the hazard of death by 44% and a 14% difference in 4-year survival favoring combination therapy. The major limitations of this trial were its lack of a TACE-alone arm and the generalizability of its findings to individual populations that have unmet needs such as those with multiple lesions larger than 3 cm and Child-Pugh class B or C. Further, this single-center trial was conducted in China, and until these results have been reproduced in individual populations representative of pathophysiology and clinical stage more commonly found in the US or Europe, the results may not be generalizable. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Bridge to Liver Transplant

For individuals who have a single hepatocellular tumor less than 5 cm or no more than three tumors each less than 3 cm in size, absence of extrahepatic disease or vascular invasion, and Child-Pugh class A or B seeking to prevent further tumor growth and to maintain candidacy for liver transplant who receive pretransplant TACE, the evidence includes multiple small prospective studies. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of comparative trials on various locoregional treatments as a bridge therapy for liver transplantation. Multiple small prospective studies have demonstrated that TACE can prevent dropouts from the transplant list. TACE has become an accepted method to prevent tumor growth and progression while individuals are on the liver transplant waiting list. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Unresectable Intrahepatic Cholangiocarcinoma

For individuals who have unresectable intrahepatic cholangiocarcinoma who receive TACE, the evidence includes several retrospective observational studies and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. RCTs evaluating the benefit of adding TACE to the standard of care for individuals with unresectable intrahepatic cholangiocarcinoma are lacking. Results of retrospective studies (noncontrolled) have shown a survival benefit with TACE over the standard of care; however, systematic reviews comparing TACE to other locoregional therapies are conflicting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

TACE for Symptomatic Unresectable Neuroendocrine Tumors

For individuals who have symptomatic metastatic neuroendocrine tumors despite systemic therapy and are not candidates for surgical resection who receive TACE, the evidence includes retrospective single-cohort studies. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs supporting the use of TACE. Uncontrolled trials have suggested that TACE reduces symptoms and tumor burden and improves hormone profiles. Generally, the response rates are over 50% and include individuals with massive hepatic tumor burden. While many studies have demonstrated symptom control, survival benefits are less clear. Despite the uncertain benefit on survival, the use of TACE to palliate the symptoms associated with hepatic neuroendocrine metastases can provide a clinically meaningful improvement in net health outcome. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Liver-Dominant Metastatic Uveal Melanoma

For individuals who have liver-dominant metastatic uveal melanoma who receive TACE, the evidence includes observational studies and reviews. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. There is a lack of evidence from RCTs assessing use of TACE. Noncomparative prospective and retrospective studies have reported improvements in tumor response and survival compared with historical controls. Given the very limited treatment response from systemic therapy and the rarity of this condition, the existing evidence may support conclusions that TACE

meaningfully improves outcomes for individuals with hepatic metastases from uveal melanoma. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Other Unresectable Hepatic Metastases

For individuals who have unresectable hepatic metastases from any other types of primary tumors (e.g., colorectal or breast cancer) who receive TACE, the evidence includes multiple RCTs, observational studies, and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple RCTs and numerous nonrandomized studies have compared TACE with alternatives in individuals who have colorectal cancer with metastases to the liver. Nonrandomized studies have reported that TACE can stabilize disease in 40% to 60% of treated individuals but whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. Two small RCTs have reported that TACE with drug-eluting beads has resulted in statistically significant improvements in response rate and progression-free survival. Whether this translates into a prolonged survival benefit relative to systemic chemotherapy alone is uncertain. For cancers other than colorectal, the evidence is extremely limited, and no conclusions can be made. Studies have assessed small numbers of individuals and the results have varied due to differences in individual selection criteria and treatment regimens used. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06353126	A Prospective, Single Arm, Exploratory Study of Using Drug-eluting Beads Transarterial Chemoembolization Prior	40	Jul 2027

NCT No.	Trial Name	Planned Enrollment	Completion Date
	to SALT Liver Transplantation in the Treatment of Hepatocellular Carcinoma		
NCT03960008	A Randomized Multi-Center Phase III Study of Individualized Stereotactic Body Radiation Therapy (SBRT) vs Trans-Arterial Chemoembolization (TACE) as a Bridge to Transplant (SBRTvsTACE) in Hepatocellular Carcinoma	196	Mar 2024
NCT04143191	Sorafenib Plus TACE Versus Sorafenib Alone as Postoperative Adjuvant Treatment for Resectable Primary Advanced HCC (SOURCE). A Phase III, Multicenter, RCT	158	Sep 2023 (unknown status)
NCT04912258	Trans-arterial Chemoembolization With Irinotecan Drug-eluting Beads Before Liver Surgery for Patients With Primary Unresectable Colorectal Liver Metastasis: A Randomized Control Trial	80	Jun 2023 (unknown status)
NCT02724540[a]	Randomized Embolization Trial for NeuroEndocrine Tumor Metastases To The Liver	162	Sept 2024
Unpublished			
NCT02936388	A Randomized Phase II Trial of Transarterial Radioembolisation with Yitrium-90 (SIRT) in Comparison to Transarterial Chemoembolisation with Cisplatin (TACE) in Patients with Liver Metastases from Uveal Melanoma	108	Dec 2022 (unknown status)

NCT: national clinical trial. [a] Denotes an industry sponsored or cosponsored clinical trial.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from one specialty medical society (two reviewers) and three academic medical centers while this policy was under review in 2012. There was general agreement that the use of TACE was medically necessary for indications in the policy;

however, reviewers were split for its use as a bridge to transplant. There was general support for the investigational policy statement for the use of TACE as neoadjuvant or adjuvant therapy in resectable HCC. Reviewers were split over the investigational policy statement to treat other liver metastases or for recurrent HCC. Four reviewers provided input on the use of TACE in unresectable cholangiocarcinoma; two reviewers considered it investigational and two others considered it investigational but also medically necessary, the latter citing data showing a survival benefit of TACE compared with supportive therapy.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network Guidelines

Hepatocellular Carcinoma

The National Comprehensive Cancer Network (NCCN) (v. 1.2024) guidelines on hepatocellular carcinoma list TACE as an option for individuals who are not candidates for surgically curative treatments or as a part of a strategy to bridge individuals for other curative therapies .[117] Arterially directed therapies, including TACE, are appropriate for individuals with unresectable or inoperable tumors that are not amenable to ablation therapy. Additionally, TACE in highly selected individuals has been shown to be safe in the presence of limited tumor invasion of the portal vein. The American Association for the Study of Liver Diseases 2023 guidelines on hepatocellular carcinoma state that patients with Barcelona Clinic Liver Cancer Stage B HCC should receive TACE (Level 1, strong recommendation).[118] Both conventional TACE and drug-eluting bead TACE are mentioned, with no preference noted between these 2 modalities.The guideline also suggests using neoadjuvant locoregional therapies (which may include TACE) for bridging to liver transplant in patients with T2 lesions, in order to prevent disease progression and prevent dropouts from the waiting list. The guidelines recommend the use of locoregional therapies, including TACE, in individuals with cirrhosis and T2 or T3 disease that is not amenable

to resection or transplantation. The American Society of Clinical Oncology (ASCO) 2024 guideline on advanced HCC states that patients with locally advanced disease may be candidates for liver-directed therapies (including TACE); however, the guideline is focused on systemic therapy so there are no recommendations regarding TACE.[119]

Intrahepatic Cholangiocarcinoma

The NCCN (v. 2.2024) guidelines on biliary tract cancers including intrahepatic cholangiocarcinoma consider arterially directed therapies, including TACE, to be treatment options for unresectable and metastatic intrahepatic cholangiocarcinoma.[117]

Neuroendocrine Tumors and Adrenal Tumors

The NCCN (v.1.2023) guidelines on neuroendocrine and adrenal tumors recommend hepatic regional therapy, including arterial embolization, chemoembolization, or radioembolization, for unresectable liver metastases (category 2B). [120]

Uveal Melanoma Cancer

The NCCN (v.1.2023) guidelines on uveal melanoma state that in individuals with disease that is confined to the liver, regional liver-directed therapies such as chemoembolization, radioembolization, or immunoembolization should be considered.[121]

Colon Cancer

The NCCN (v. 2.2024) guidelines on colon cancer recommend TACE only for clinical trials.[122] The American Society of Clinical Oncology (ASCO, 2020) resource-stratified guidelines on late-stage colorectal cancer state that individuals with unresectable liver metastases may receive TACE (weak recommendation).[123] However, this recommendation should only be implemented in centers with expertise in the technique, after multidisciplinary review, or in the context of a clinical trial. The 2022 guidelines for metastatic colorectal cancer from ASCO do not address TACE.[124]

Breast Cancer

The NCCN (v. 4.2024) guidelines on breast cancer do not address TACE as a treatment option for breast cancer metastatic to the liver.[125]

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

Chemoembolization for hepatic tumors is a medical procedure and, as such, is not subject to regulation by the US Food and Drug Administration. However, the embolizing agents and drugs are subject to US Food and Drug Administration approval.

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History

Date	Comments
10/01/19	New policy, approved September 5, 2019. This policy replaces policy 8.01.505 (originally effective June 1999) which is now deleted. Policy created with literature review through May 2019. Transcatheter hepatic arterial chemoembolization may be considered medically necessary when criteria are met; considered investigational when criteria are not met.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020.
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.
10/01/20	Annual Review approved September 1, 2020. Policy updated with literature review through June 2020; references added. Added "in combination" with radiofrequency ablation for resectable or unresectable hepatocellular carcinoma to the investigational policy statement for clarity; otherwise policy statements unchanged.
06/01/21	Update Related Policies. Corrected Renumbered Policy 8.01.431 to 8.01.43
10/01/21	Annual Review, approved September 23, 2021. Policy updated with literature review through June 3, 2021; references added. Policy statements unchanged.

Date	Comments
10/01/22	Annual Review, approved September 12, 2022. Policy updated with literature review through May 20, 2022; reference added and guidelines updated. Minor editorial refinements to policy statements; intent unchanged.
06/15/23	Update to Related Policies. 8.01.43 is replaced with 8.01.521 Radioembolization for Primary and Metastatic Tumors of the Liver.
10/01/23	Annual Review, approved September 11, 2023. Changed the wording from "patient" to "individual" throughout the policy for standardization. Policy updated with literature review through May 23, 2023; reference added and guidelines updated. Policy statements unchanged.
10/01/24	Annual Review, approved September 23, 2024. Policy updated with literature review through May 21, 2024; references added. Minor editorial refinements to policy statements to specify intrahepatic cholangiocarcinoma.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.