Echocardiographic assessment of myocardial strain for cancer patients.

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Policy contains: Chemotherapy side effects; deformation imaging; echocardiograph strain imaging; myocardial strain; speckle tracking

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Coverage policy

Echocardiographic assessment of myocardial strain to measure cardiac impairment in cancer patients treated with chemotherapy is clinically proven and, therefore, medically necessary. Left ventricular ejection fraction should be measured just before, just after, and 3 - 6 months after chemotherapy for breast cancer or childhood cancer that has the potential for either Type 1 cardiotoxicity (such as anthracyclines) or Type 2 cardiotoxicity (such as trastuzumab) (Bovelli, 2010; Plana, 2014; Smiseth, 2016). For drugs with the potential for Type I toxicity, echocardiographic imaging, including strain, is recommended at completion of therapy and six months later. For drugs with the potential for Type II toxicity, echocardiography with strain imaging is recommended every three months during therapy (Plana, 2014).
For patients receiving anthracyclines and/or trastuzumab after baseline clinical evaluation and heart echocardiography, routine clinical follow-ups and heart echocardiography are recommended every three months for the first year of therapy.

For anthracyclines in particular, a repeat echocardiography is recommended at a cumulative dose of 240 mg/m², or earlier if clinical symptoms and/or an increase in cardiac enzymes is observed.

For higher anthracycline doses, routine echocardiograms are recommended before each anthracycline cycle.

For less cardiotoxic chemotherapy, follow-up assessments (including echocardiograms) should be individualized.

Long-term clinical follow-up is mandatory for anthracyclines. Routine heart echocardiographs are recommended at 6, 24, and 36 months after the last anthracycline cycle.

For patients who received anthracyclines before adolescence (< 15 years old) or those exposed to high doses (> 240 mg/m²), follow-up monitoring (including echocardiographs) should extend to four to 10 years after therapy (Koutsoukis, 2018).

**Limitations**

All other uses of echocardiographic assessment of myocardial strain may or may not be medically necessary depending on the purpose of the test.

**Alternative covered services**

Various uses of echocardiography.

**Background**

The chance of cardiotoxicity after chemotherapy is not a rare one, especially for breast cancer and childhood cancer. One study found that 15% of breast cancer patients who underwent chemotherapy (anthracycline and trastuzumab) developed heart failure and cardiomyopathy, a 40% higher rate than matched breast cancer cohorts who did not receive chemotherapy (Bowles, 2012).

Myocardial strain imaging, also known as echocardiographic strain imaging or deformation imaging, reflects left ventricular function. Longitudinal and radial strain increases with heart rate, and decreases with age (Kuznetsova, 2008). Echocardiographic assessment of myocardial strain is a relatively new means of assessing myocardial function. This technology, introduced in the late 1990s, is one of the diagnostic methods considered potentially more advanced than conventional echocardiography, as it is able to evaluate components of cardiac function, including those functions not visually accessible.

Strain and strain-rate imaging are often effective means of measuring prognosis of cardiac disease, along with effects of various therapies on the heart (Dandel, 2009). Strain is another means of describing “stretching” of the myocardial system — a lengthening, shortening, or thickening as a measure of regional left ventricular function — while strain rate is the rate of this deformity.

Strain imaging provides greater understanding of the pathophysiology of cardiac ischemia and infarction, primary diseases of the myocardium, assessment of the dyssynchrony for cardiac resynchronization therapy, effects of valve disease on myocardial function, and the mechanics of diastolic function. Most labs use echocardiographic visual assessment of wall motion for clinical use. Strain imaging has been generally used in research, but is becoming more commonly used in practice over time.
The original myocardial strain technique uses tissue Doppler imaging to assess longitudinal strain from apical windows with left ventricular shortening and lengthening with Doppler scan lines. A newer technique uses “speckle tracking,” a digital imaging method that creates blocks of pixels to identify strain vectors; three-dimensional speckle tracking is now available as well (Geyer, 2010; Gorscan, 2011).

Strain imaging incorporates complex geometric aspects of left ventricular contraction in a more comprehensive manner than standard testing of the left ventricle. Thus, strain imaging, which now is available in many laboratories, is viewed by some to have greater advantages than other types of tests assessing left ventricular ejection fraction (Januzzi, 2017).

The high prevalence of cancer and the growing number of chemotherapy drugs used to treat cancer patients make precise measurements of various organ functions a vital part of treatment. In particular, chemotherapy can be cardiotoxic; treatment-related cardiac death is the most prevalent non-cancer cause of death in adult survivors of childhood cancer (Armstrong, 2015). A study of 16,456 adults with non-metastatic breast cancer identified 4.2% who had cardiotoxicity after chemotherapy (Henry, 2018).

Patients with heart failure after chemotherapy are treated according to standard heart failure protocols. When the reduction in left ventricular ejection fraction during chemotherapy is established, it sometimes may not be in time for effective treatment. This is especially true in cases when global longitudinal strain reduction is clinically significant — greater than 15%. A general requirement is that patients should have left ventricular ejection fraction measured just before, just after, and six months after chemotherapy (Smiseth, 2016).

The most commonly measured cardiac functions in post-chemotherapy patients are left ventricular systolic function and left ventricular ejection fraction. Echocardiographic measures of left ventricular function are critical in clinical decision making, with global longitudinal strain emerging as a promising tool in informing and facilitating the selection of cancer treatment and optimizing cardiovascular outcomes (Liu, 2018).

Chemotherapy-related cardiac dysfunction was originally measured by periodic surveillance of left ventricular ejection fraction through nuclear imaging, magnetic resonance imaging, and other means. Echocardiography now has surpassed these modalities as the preferred method of measuring cardiac dysfunction, as it is more accurate, available, and portable, and less radioactive (Abdel-Qadir, 2015).

Studies measuring cardiac dysfunction have typically focused on breast cancer survivors or adult survivors of childhood cancer. Various chemotherapy drugs known to cause cardiovascular side effects have been studied, including but not limited to:

- Anthracyclines, including doxorubicin (Adriamycin) and epirubicin (Ellence).
- Human epidermal growth factor receptor type 2 monoclonal antibody.
- Trastuzumab (Herceptin).

Many reports on myocardial strain imaging for chemotherapy patients are not controlled trials assessing which type of echocardiography best detects cardiovascular problems; they merely address the efficacy of a particular form of echocardiography. In addition to chemotherapy patients, myocardial strain imaging can be used for other conditions, including sepsis/septic shock, pulmonary hypertension, and various cardiovascular disorders.

**Findings**

Some professional societies have produced guidelines on types of echocardiography, including assessment of myocardial strain for chemotherapy drugs with Type 1 or 2 cardiotoxicity. One is from the European Society for
Medical Oncology (Bovelli, 2010). Another is from the American Society of Echocardiography and European Association of Cardiovascular Imaging (Plana, 2014). Both extol the benefits of echocardiography due to its ability to assess more than ventricular function in a relatively low-cost, noninvasive, and radiation-free manner.

A more recent guideline from a panel of European experts recommends an echocardiogram with speckle tracking before potentially cardiotoxic chemotherapy; an echocardiogram every three months in the first year of therapy if anthracyclines or trastuzumab is used; and routine heart echocardiograms at 6, 24, and 36 months after the last anthracycline cycle (Koutsoukis, 2018). The American College of Cardiology issued a report concluding that while strain imaging can be used to evaluate deformation of the myocardium, it is best utilized as a research tool with limited everyday clinical application (Safi, 2017). The College also issued a guideline stating that myocardial strain imaging by speckle or tissue Doppler were appropriate for four indications (below), but not for any of 77 other indications:

- Initial evaluation prior to exposure to medications/radiation that could result in cardiotoxicity/heart failure;
- Re-evaluation (one year) in a patient previously or currently undergoing therapy with potentially cardiotoxic agents;
- Periodic re-evaluation in a patient undergoing therapy with cardiotoxic agents with worsening symptoms; and
- Evaluation of suspected hypertrophic cardiomyopathy (Doherty, 2019).

The move towards specialized echocardiographs began as early as 2008, as experts recommended that Doppler-based myocardial deformation imaging be used to monitor cardiac function during chemotherapy, instead of conventional echocardiography (Jurcut, 2008). One relatively early study used two-dimensional echocardiography to document lower global myocardial strain, strain rates, and time to peak systolic strain in long-term childhood cancer survivors versus healthy controls, and speculated that two-dimensional echocardiography might provide superior results to conventional echocardiography (Mavinkurve-Groothuis, 2010).

Speckle tracking is the most widely used technique to detect strain (Collier, 2017). One study discovered that longitudinal speckle strain had greater power to predict mortality ($P < .0001$) than did ejection fraction ($P < .03$) or wall motion score index ($P < .01$) (Stanton, 2009).

Another early study stated that myocardial strain imaging had the potential to detect changes in cardiac function from chemotherapy earlier than conventional echocardiography (Stoodley, 2011a). The same research team documented that two-dimensional myocardial strain imaging detected changes in left ventricular systolic function immediately after chemotherapy in 52 women with breast cancer (Stoodley, 2011b).

Several more recent systematic reviews and meta-analyses that compared efficacy (in terms of myocardial strain) of different types of echocardiography updated earlier findings. Some include cancer patients, while others assess other disorders.

Non-cancer patients

- A systematic review and meta-analysis of eight studies ($n = 794$) patients with sepsis-induced myocardial dysfunction compared speckle tracking of global longitudinal strain and standard left ventricular ejection tracking testing as a predictor of mortality. A significant association was identified between worse left ventricular function and global longitudinal strain values and mortality ($P = .02$), but not for left ventricular ejection fraction tracking and mortality ($P = .83$) (Sanfilippo, 2018).

- A meta-analysis of 10 studies ($n = 458$) found that in five studies, compared with healthy controls, patients with arrhythmogenic right ventricular cardiomyopathy, which can lead to sudden death, had a significantly lower myocardial strain (17% versus 30% ($P < .001$) (Qasem, 2016).
A systematic review of seven studies (n = 3,138) used speckle tracking echocardiography for myocardial strain to assess effectiveness for prognostication. In five studies, global longitudinal strain predicted the development of adverse left ventricular fraction (P values varied from < .05 to < .001), and in four studies, it also predicted the development of major adverse cardiac events (P < .006 to P < .05); authors concluded it is a predictor of poor prognosis (Sheyte, 2015).

A meta-analysis of 10 studies (n = 486) of patients with normal echocardiograms and with no cardiopulmonary disease or risk factors showed the weighted estimate of right ventricular free wall strain using tissue Doppler alone and with speckle tracking, were equal at -27, estimating a right ventricular strain range in subjects without cardiopulmonary disease (Fine, 2015).

Cancer patients

A systematic review found that for 1,504 chemotherapy patients, tissue Doppler strain imaging most consistently detected early myocardial changes during treatment, while speckle tracking echocardiography most consistently detected peak systolic global longitudinal strain (Thavendiranathan, 2014).

A study of 1,820 adult survivors of pediatric cancer, most of whom were treated with anthracycline chemotherapy, reviewed patients with normal left ventricular ejection fractions after three-dimensional echocardiography; 28.0% had evidence of cardiac dysfunction when global longitudinal strain was used, compared to just 8.7% when American Society of Echocardiography-graded diastolic assessment was used (Armstrong, 2015).

A systematic review and meta-analysis of 14 studies of children, adolescents, and young adults addressed changes in myocardial dysfunction after anthracycline therapy for childhood cancer. Global longitudinal strain abnormalities are common during and just after chemotherapy, but changes in global circumferential strain/global radial strain occur after long-term follow-up. Authors conclude myocardial strain by echocardiography is useful for evaluating subclinical myocardial injury (Tuzovic, 2018).

A systematic review of six studies (n = 2,545) of subjects with cancer documented that, after a multi-gated acquisition scan or echocardiograph before treatment, 2.5% had abnormal left ventricular ejection fraction, and 1.6% had a change in chemotherapy decision. Authors recommend efforts to better identify low-risk patients that do not need left ventricular assessment at baseline, preventing delay in chemotherapy administration (O’Brien, 2019).

A systematic review and meta-analysis of 16 studies of breast cancer patients given anthracyclines or trastuzumab showed significant reductions in two-dimensional left ventricular ejection fraction and speckle tracking echocardiography parameters early in chemotherapy. Peak systolic global longitudinal strain was the most consistently detected early myocardial change, upholding the role of monitoring and starting cardioprotective treatment (Bergamini, 2019).

References

On December 27, 2019, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “myocardial strain,” “chemotherapy,” “echocardiography,” “tissue doppler,” “Doppler,” “echocardiograph strain imaging,” “deformation imaging,” and “speckle tracking.” We included the best available evidence according to established evidence hierarchies
(typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.


**References**

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**Policy updates**

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