Using Adversarial Images to Assess the Robustness of Deep Learning Models Trained on Diagnostic Images in Oncology

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PURPOSE Deep learning (DL) models have rapidly become a popular and cost-effective tool for image classification within oncology. A major limitation of DL models is their vulnerability to adversarial images, manipulated input images designed to cause misclassifications by DL models. The purpose of the study is to investigate the robustness of DL models trained on diagnostic images using adversarial images and explore the utility of an iterative adversarial training approach to improve the robustness of DL models against adversarial images.

METHODS We examined the impact of adversarial images on the classification accuracies of DL models trained to classify cancerous lesions across three common oncologic imaging modalities. The computed tomography (CT) model was trained to classify malignant lung nodules. The mammogram model was trained to classify malignant breast lesions. The magnetic resonance imaging (MRI) model was trained to classify brain metastases.

RESULTS Oncologic images showed instability to small pixel-level changes. A pixel-level perturbation of 0.004 (for pixels normalized to the range between 0 and 1) resulted in most oncologic images to be misclassified (CT 25.6%, mammogram 23.9%, and MRI 6.4% accuracy). Adversarial training improved the stability and robustness of DL models trained on oncologic images compared with naive models ([CT 67.7% vs 26.9%], mammogram [63.4% vs 27.7%], and MRI [87.2% vs 24.3%]).

CONCLUSION DL models naively trained on oncologic images exhibited dramatic instability to small pixel-level changes resulting in substantial decreases in accuracy. Adversarial training techniques improved the stability and robustness of DL models to such pixel-level changes. Before clinical implementation, adversarial training should be considered to proposed DL models to improve overall performance and safety.
oncologic imaging modalities. We established the performance of the DL models and then tested model output stability in response to adversarial images with different degrees of pixel-level manipulation. We then tested the utility of techniques to defend the DL models against adversarial images. This research has direct application to the use of DL image interpretation algorithms, as it provides quantitative testing of their vulnerability to small input variations and determines whether there are strategies to reduce this weakness.

METHODS

Ethics Declaration
The research was conducted in accordance with the Declaration of Helsinki guidelines and approved by the Yale University Institutional Review Board (Protocol ID: HIC#2000027592). Informed consent was obtained from all participants in this study.

Data Sets
We examined the behavior of DL algorithm outputs in response to adversarial images across three medical imaging modalities commonly used in oncology—CT, mammography, and MRI. For each imaging modality, a separate DL classification model was trained to identify the presence or absence of malignancy when given a diagnostic image. Each data set was split into a training set and a testing set in a 2:1 ratio. CT imaging data consisted of 2,600 lung nodules from the Lung Image Database Consortium and Image Database Resource Initiative (LIDC-IDRI) collection. The data set contains 1,018 thoracic CT scans collected from 15 clinical sites across the United States. Lung nodules used for DL model training were identified by experienced thoracic radiologists. The presence of malignancy was based on associated pathologic reports. For patients without pathologic confirmation, malignancy was based on radiologist consensus.

Mammography imaging data consisted of 1,696 lesions from the Curated Breast Imaging Subset of Digital Database for Screening Mammography (CBIS-DDSM). The CBIS-DDSM contains mammograms from 1,566 patients at four sites across the United States. Mammographic lesions used for DL model training were obtained on the basis of algorithmically derived regions of interest based on clinical metadata. The presence of malignancy was based on verified pathologic reports.

MRI data consisted of brain MRIs from 831 patients from a single-institution brain metastases registry. The presence or absence of a malignancy was identified on 4,000 brain lesions seen on MRI. Regions of interest were identified by a multidisciplinary team of radiation oncologists, neurosurgeons, and radiologists. Presence of cancer was identified on the basis of pathologic confirmation or clinical consensus. To compare the relative vulnerability of DL models trained on oncologic images compared with nonmedical images, two additional DL classification models were trained on established nonmedical data sets. The MNIST data set consists of 70,000 handwritten numerical digits. The CIFAR-10 data set includes 60,000 color images of 10 nonmedical objects.

All images were center-cropped and resized, and pixel values were normalized to the range [0, 1]. For each medical data set, the classes (cancer and noncancer) were balanced, and data were augmented using simple data augmentations: horizontal and vertical flips as well as random rotations with angles ranging between −20° and 20°.

We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline, and a TRIPOD checklist was included (Data Supplement).

Models
For all DL classification models, we used a pretrained convolutional neural network with the VGG16 architecture. Models were fine-tuned in Keras using Stochastic Gradient Descent. Details regarding model architecture and hyperparameter selection for DL model training are provided in the Data Supplement.

Adversarial Image Generation
Three commonly used first-order adversarial image generation methods—Fast Gradient Sign Method (FGSM), Basic Iterative Method (BIM), and Projected Gradient

CONTEXT

Key Objective
Are deep learning (DL) models trained to classify diagnostic images in oncology more vulnerable to adversarial images than natural images?

Knowledge Generated
We found that DL classification models trained on oncologic images were more susceptible to adversarial images than natural images. Additionally, we found that adversarial image sensitivity can be leveraged to improve DL model robustness.

Relevance
Adversarial images represent a potential barrier to end-to-end implementation of DL models within clinical practice. Nevertheless, adversarial images can also be used to improve the overall robustness of DL models within clinical oncology.
Descent (PGD)—were used to create adversarial images on the medical and nonmedical image data sets (Fig 1). Each method aims to maximize the DL model’s classification error while minimizing the difference between the adversarial image and original image. All the adversarial image generation methods are bounded under a predefined perturbation size $\varepsilon$, which represents the maximum change to pixel values of an image. Vulnerability to adversarial images was assessed by comparing changes in model performance compared with baseline (without any adversarial images) under various perturbation sizes.

The single-step FGSM attack perturbs the original example by a fixed amount along the direction (sign) of the gradient of adversarial loss.$^{15}$ Given input image $x$, perturbation size, loss function $J$, and target label $y$, the adversarial image $x_{adv}$ can be computed as

$$\quad x_{adv} = x + \varepsilon \cdot \text{sign}(\nabla_x J(x, y)).$$

(1)

BIM iteratively perturbs the normal example with smaller step size and clips the pixel values of the updated adversarial example after each step into a permitted range.$^{12}$

$$\quad x^t = \text{Clip}_{x,\varepsilon}(x^{t-1} + \alpha \cdot \text{sign}(\nabla_x J(x^t, y))).$$

(2)

Known as the strongest first-order attack, PGD iteratively perturbs the input with smaller step size and after each iteration, the updated adversarial example is projected onto the $\varepsilon$-ball of $x$ and clipped onto a permitted range.$^{18}$

$$\quad x^t = \prod(x^{t-1} + \alpha \cdot \text{sign}(\nabla_x J(x^t, y))).$$

(3)

Additional information regarding adversarial image generation methods and equation parameters is provided in the Data Supplement.

**Susceptibility of DL Models to Adversarial Images**

We investigated the DL model performance using FGSM, PGD, and BIM adversarial image generation methods across different levels of pixel perturbation. To evaluate the performance of the DL models on adversarial images, we generated adversarial test sets by applying adversarial attacks on the original clean test sets. We measured relative susceptibility to adversarial images by determining the smallest perturbation $\varepsilon$ required for adversarial images to generate a different output. DL models that required larger pixel-level perturbations are likely to be more robust and have higher levels of stability suitable for clinical implementation. Conversely, models that change outputs in response to small pixel-level perturbations are inherently unstable and potentially less generalizable across different clinical settings and patient populations.

**Adversarial Training to Improve Model Robustness**

One proposed defense mechanism to prevent negative effects of adversarial images is adversarial training, which aims to improve model robustness by integrating adversarial samples into DL model training.$^{18,20}$ By training on both adversarial and normal images, the DL model learns to classify adversarial samples with higher accuracy compared with models trained on only normal samples. We used a multistep PGD adversarial training to increase the robustness of our DL models against adversarial attacks. In each batch, 50% of training samples were normal images, and the other 50% were adversarial images generated by PGD attack. We used the PGD attack for adversarial training because it is considered the strongest first-order attack, and past research has demonstrated that models adversarially trained with PGD were robust against other first-order attacks.$^{18}$ The hyperparameters for adversarial training are detailed in the Data Supplement. We investigated the effectiveness of our iterative adversarial training approach on the DL models trained on medical images. We measured the effectiveness of adversarial training by comparing model accuracy on adversarial samples of varying perturbation sizes before and after adversarial training.

**Image-Level Adversarial Image Sensitivity and Model Performance**

We examined each individual image’s adversarial sensitivity, as measured by the level of pixel-level perturbation necessary for DL model prediction to change compared with an unperturbed image. We hypothesized that images requiring smaller pixel-level adversarial perturbations to change DL model predictions were also the images most likely to be misclassified by the model under normal conditions absent of adversarial attack (compared with other clean images). We identified the 20% of images most vulnerable to adversarial perturbation and excluded them from the test set. We then tested the performance of the DL model on the clean version of the reduced test set. If the images most sensitive to adversarial perturbation are also more likely to be misclassified as clean images by the DL model under normal conditions, the model performance on the clean version of the reduced test set would be expected to improve from the model performance on the clean version of the original test.

The proposed networks were implemented in Python 2.7 using TensorFlow v1.15.3 framework.$^{28}$ Adversarial images were created using the Adversarial Robustness Toolbox v1.4.1.$^{29}$ The code to reproduce the analyses and results is available online at GitHub.$^{30}$

**RESULTS**

**Susceptibility of DL Models to Adversarial Images**

Both medical and nonmedical DL models were highly susceptible to misclassification of adversarial images, resulting in decreases in model accuracy (Fig 2). Medical DL models appeared substantially more vulnerable to adversarial images compared with nonmedical DL algorithms. All three medical DL models required smaller
pixel-level perturbations to decrease model accuracy compared with nonmedical DL models (Fig 2). For example, adversarial images generated using the PGD method (perturbation = 0.002) resulted in a DL model accuracy of 26.9% for CT (–48.5% from baseline), 27.7% for mammogram (–48.8% from baseline), and 24.3% for MRI (–61.8% from baseline). By contrast, adversarial images generated using the same methods/parameters did not cause substantial changes in performance for the MNIST (–0.05% from baseline) or CIFAR-10 (–4.2% from baseline) trained models (Table 1). For the medical DL models, adversarial images generated using smaller pixel-level perturbations ($\epsilon < 0.004$) resulted in misclassification of a majority of images, whereas nonmedical DL models required much larger pixel perturbations ($\epsilon > 0.07$ for MNIST and $\epsilon > 0.01$ for CIFAR-10) for similar levels of misclassification (Table 1).

**Adversarial Training to Improve Model Robustness**

Adversarial training led to increased robustness of DL models when classifying adversarial images for both medical and nonmedical images (Fig 3). Compared with baseline trained models, adversarial trained DL models caused absolute accuracy of the model on adversarial images to increase by 42.9% for CT (67.7% v 26.9%), 35.7% for mammogram (63.4% v 27.7%), and 73.2% for MRI (87.2% v 24.3%; Data Supplement). Despite adversarial training, DL models did not reach baseline accuracy, suggesting adversarial training as only a partial solution to improve model robustness. Adversarial training became
less effective when attempting to defend against adversarial images that possessed greater pixel perturbations.

**Image-Level Adversarial Image Sensitivity and Model Performance**

Using image-level adversarial sensitivity, we were able to identify images most at risk for misclassification by the DL models and improve overall model performance across all diagnostic imaging modalities. Excluding the images in which the smallest pixel perturbations changed DL model outputs increased the absolute accuracy of DL models by 5.9% for CT, 3.7% for mammogram, and 5.2% for MRI (Table 2).

**DISCUSSION**

As the role of diagnostic imaging increases throughout clinical oncology, DL represents a cost-effective tool to supplement human decision making and aid in image analysis tasks.\(^\text{31-33}\) However, instability of DL model outputs can limit the performance and generalizability on large-scale medical data sets and hinder clinical utility. Evaluating a proposed DL model’s susceptibility to adversarial images represents a way to identify the most robust DL models versus those at risk for erratic performance. In this study, we found that DL models trained on medical images were particularly unstable to perturbation from adversarial images resulting in significant decreases in expected performance. Moreover, we found diagnostic images within oncology to be more vulnerable to such misclassification compared with DL models trained on nonmedical images. Specifically, compared with nonmedical images, all three diagnostic imaging modalities required substantially smaller perturbation to reduce model performance. Furthermore, we found that adversarial training methods commonly used on nonmedical imaging data sets are effective at improving DL model stability to such pixel-level changes. Finally, we showed that identifying images most susceptible to adversarial image attacks maybe helpful in improving overall robustness of DL models on medical images.

Several recent works have found that state-of-the-art DL architectures perform poorly on medical imaging analysis tasks when classifying adversarial images.\(^\text{14,34-38}\) Our work extends the findings of previous studies by evaluating performance across three common oncologic imaging modalities used for cancer detection. Additionally, we found that CT, mammography, and MRI images exhibit substantial vulnerability to adversarial images even with small pixel-level perturbations (<0.004). We also show that DL models exhibited different levels of sensitivity to adversarial images across different imaging modalities. Furthermore, although most previous studies used only one fixed perturbation size for adversarial image attack, we varied perturbation size along a broad range to examine the relationship between model performance and attack strength.

In addition, our results corroborate previous work, which showed that DL models trained on medical images are more vulnerable to misclassifying adversarial images compared with similar DL models trained on nonmedical images.\(^\text{14,39}\) By using MNIST and CIFAR-10 as a control and applying the same attack settings to DL models for all data sets, we determined that DL models for medical

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**TABLE 1. Effects of Adversarial Attacks of Varying Perturbation Sizes on Model Classification Accuracy**

| Attack | Perturbation Size ε | CT Accuracy (%) | Mammogram Accuracy (%) | MRI Accuracy (%) | MNIST Accuracy (%) | CIFAR-10 Accuracy (%) |
|--------|---------------------|----------------|-----------------------|----------------|------------------|---------------------|
| Baseline |                     | 75.41          | 76.43                 | 93.64          | 99.13            | 86.13               |
| FGSM  | 0.001               | 51.98          | 46.96                 | 77.27          | 99.05            | 85.32               |
|       | 0.002               | 34.62          | 30.00                 | 56.36          | 99.05            | 82.39               |
|       | 0.004               | 31.12          | 24.46                 | 43.03          | 99.04            | 74.29               |
|       | 0.006               | 31.59          | 23.93                 | 40.38          | 98.96            | 65.27               |
| PGD   | 0.001               | 41.84          | 45.36                 | 61.36          | 99.06            | 85.29               |
|       | 0.002               | 26.92          | 27.68                 | 24.32          | 99.05            | 81.93               |
|       | 0.004               | 25.64          | 23.93                 | 6.36           | 99.01            | 71.90               |
|       | 0.006               | 25.64          | 23.57                 | 6.36           | 98.92            | 59.98               |
| BIM   | 0.001               | 44.99          | 46.07                 | 64.24          | 99.06            | 85.32               |
|       | 0.002               | 27.74          | 28.57                 | 29.02          | 99.05            | 82.06               |
|       | 0.004               | 25.87          | 23.93                 | 6.44           | 99.01            | 72.84               |
|       | 0.006               | 25.76          | 23.57                 | 6.36           | 98.93            | 62.28               |

**NOTE.** Adversarial samples were created by FGSM, BIM, and PGD with increasing $L_\infty$ maximum perturbation size $\varepsilon$. Models for medical data sets (CT, mammogram, and MRI) required smaller attack perturbation sizes than models for nonmedical data sets (MNIST and CIFAR-10) for attacks to be generally effective.

**Abbreviations:** BIM, Basic Iterative Method; CT, computed tomography; FGSM, Fast Gradient Sign Method; MRI, magnetic resonance imaging; PGD, Projected Gradient Descent.
images were much more susceptible to misclassifying adversarial images than DL models for nonmedical images. One reason for this behavior could be that medical images are highly standardized, and small adversarial perturbations dramatically distort their distribution in the latent feature space.40,41 Another factor could be the overparameterization of DL models for medical image analysis, as sharp loss landscapes around medical images lead to higher adversarial vulnerability.14

In the past, adversarial training on medical DL models has shown mixed results. In some studies, adversarial training improved DL model robustness for multiple medical imaging modalities such as lung CT and retinal optical coherence tomography.40,42-44 By contrast, Hirano et al45 found that adversarial training generally did not increase model robustness for classifying dermatoscopic images, optical coherence tomography images, and chest x-ray images. The difference in effectiveness of adversarial training can be attributed to differences in adversarial training protocols (eg, single-step vs iterative approaches). It is important to note that even in studies where adversarial training showed success in improving model robustness, the results were still suboptimal, as the risk of misclassification increases with perturbation strength even after adversarial training. This is expected as adversarial training, although capable of improving model accuracy on adversarial examples, has limits in effectiveness against strong attacks even on nonmedical image data sets.18

Our work applied an iterative adversarial training approach to DL models for lung CTs, mammograms, and brain MRIs, demonstrating substantial improvement in model robustness for all imaging modalities. The effectiveness of adversarial training was highly dependent on the hyperparameters of adversarial training, especially the perturbation size for attack. Although too-small perturbation sizes limit the increase in model robustness postadversarial training, increasing the perturbation size beyond a certain threshold prevents the model from learning during training, causing poor model performance on both clean and adversarial samples. Our work demonstrated how the performance of the DL model postadversarial training is inversely proportional to the perturbation size of the adversarial samples on which the model is evaluated. Although adversarial training is effective in defending against weaker attacks with smaller perturbation magnitudes, it showed less success with attacks that altered pixels more substantially. Although adversarial training proved successful at improving model performance on adversarial examples, our results were still far from satisfactory. One contributing factor is that medical images have fundamentally differently properties than nonmedical images.14,40 Thus, adversarial defenses...
well suited for nonmedical images may not be generalizable to medical images.

We also showed that image-level adversarial sensitivity, defined by the level of adversarial perturbation necessary to change image class predicted by model, is a useful metric for identifying normal images most at risk for misclassification. This has potentially useful clinical implications as we can improve the robustness of DL models by excluding such ‘high-risk’ images from DL model classification and instead providing them to a trained radiologist for examination.

There are several limitations to our study. First, we only used two-class medical imaging classification tasks. Thus, our findings might not generalize to multiclass or regression problems using medical images. Given that many medical diagnostic problems involve a small number of classes, our findings are likely still widely applicable to a large portion of medical imaging classification tasks. Our study used only first-order adversarial image generation methods rather than higher-order methods, which have been shown to be more resistant against adversarial training. Although most commonly used adversarial image generation methods are first-order, there is still need for additional research on how to defend DL models for medical images against higher-order methods. A final limitation is that we used traditional supervised adversarial training to improve model robustness, whereas other nuanced methods such as

TABLE 2. Classification Accuracy (%) of VGG16 Model on the Original Test Set and the Test Set Excluding the 20% of Test Images Most Susceptible to Adversarial Attack

| Diagnostic Image Modality | Model Accuracy (%) | Model Accuracy (%) Adversarially Aware Test Set | Change in Model Accuracy (%) |
|---------------------------|-------------------|-----------------------------------------------|-----------------------------|
| CT                        | 75.41             | 81.31                                         | 5.90                        |
| Mammogram                 | 76.43             | 80.13                                         | 3.70                        |
| MRI                       | 93.64             | 98.82                                         | 5.18                        |

NOTE. Images were excluded if PGD attack with perturbation size less than a certain threshold was sufficient to change the model prediction on the image. That threshold perturbation size was 0.0003 for CT, 0.00025 for mammogram, and 0.0006 for MRI.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PGD, Projected Gradient Descent.
semisupervised adversarial training and unsupervised adversarial training exist.\textsuperscript{40,47,48} Although we demonstrated that supervised adversarial training is an effective method to improve model performance on adversarial examples, an interesting direction for future work would be to compare the utility of supervised adversarial training with that of semisupervised or unsupervised adversarial training on DL models for medical images.

In conclusion, in this work, we used adversarial images to explore the stability of DL models trained on three common diagnostic imaging modalities used in oncology. Our findings suggest that DL models trained on diagnostic images are vulnerable to pixel-level changes, which can substantially change expected performance. Specifically, we found that vulnerability to adversarial images can be a useful method to identify DL models that are particularly unstable in their classifications. Additionally, we found that adversarial image training may improve the stability of DL models trained on diagnostic images. Finally, we found that image-level adversarial sensitivity is a potential way to identify image samples that may benefit from human classification rather than DL model classification. By shedding light on the stability of DL models to small pixel changes, the findings from this paper can help facilitate the development of more robust and secure medical imaging DL models that can be more safely implemented into clinical practice.

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