Volume-based Performance not Guaranteed by Promising Patch-based Results in Medical Imaging

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Abstract

Whole-body MRIs are commonly used to screen for early signs of cancers. In addition to the small size of tumours at onset, variations in individuals, tumour types, and MRI machines increase the difficulty of finding tumours in these scans. Using patches, rather than whole-body scans, to train a deep-learning-based segmentation model, with a custom compound patch loss function, several augmentations, and additional synthetically generated training data to identify areas where there is a high probability of a tumour provided promising results at the patch-level. However, applying the patch-based model to the entire volume did not yield great results despite all of the state-of-the-art improvements, with over 50% of the tumour sections in the dataset being missed. Our work highlights the discrepancy between the commonly used patch-based analysis and the overall performance on the whole image and the importance of focusing on the metrics relevant to the ultimate user, in our case, the clinician. Much work remains to be done to bring state-of-the-art segmentation to clinical practice of cancer screening.

1 Introduction

Finding small anomalies in large images is challenging for many reasons. Especially within the medical imaging domain, the low signal-to-noise ratio, lack of large amounts of data, paucity of positive cases (anomalies such as cancer), heterogeneity in the data and the anomalies, and variation in expert labels exacerbate the effectiveness of machine learning approaches in detecting anomalies. Patch-based approaches are some of the commonly used methods in the field to boost the success of detection [1, 2, 3, 4].

In pediatric whole-body MRIs (wbMRIs), early detection of cancers at onset (i.e. at a very small size within the body) is crucial for a good prognosis, especially in children with cancer predisposition syndromes [5]. Variations in the child, the type of cancer, and the type of MRI must be considered during the evaluation of wbMRIs. A screening tool that can be used by radiologists and oncologists with varying expertise to assist them in finding regions where there is high likelihood of a tumour can save time and improve tumour detection capabilities.

Deep-learning-based segmentation approaches have seen great advancements in recent years, especially within the field of medical imaging. In this paper, we present our modified patch-based approach for tumour segmentation to overcome the challenges with low amounts of positive cases (i.e. cancers) and the vast data heterogeneity. Even after attempting to address these issues (see Table 1 in Section 3) by splitting the data into patches, using the U-Net segmentation model, training with asymmetric unified focal loss, dice loss, contour perimeter loss, and contour difference loss (see Section 5), selecting different proportions of positive cases and negative cases in the dataset, utilizing data augmentations, and adding synthetic training data to the dataset, there is still room for improvement in the tumour segmentation performance in wbMRIs.

Our results indicate the need to consider a combination of metrics to understand how patch-based performance and overall performance affect each other and that given a set of patches related to a larger task, the patch-based performance may not be fully indicative of how the overall performance may turn out.

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2 Related Work

There has been a lot of work in recent years in tumour detection and localization in MRIs, however the amount of work in pediatric whole-body MRIs focused on finding tumours at onset (i.e. very small) in any part of the body continues to be rare. Non-segmentation-based deep learning techniques for tumour detection and localization include classification [6, 7, 8, 9], anomaly detection with generative adversarial networks [10, 11, 12, 13, 14] or variational auto-encoders [15, 16, 17], or a combination of these approaches [18, 19]. Segmentation-based deep learning techniques for tumour detection and localization [20, 21, 22] perform well within organ-specific domains due to the well-defined nature of the body regions and anomalies (i.e tumours). However, all of these methods have trouble in domains with very little positive case data and vast data heterogeneity, especially when the size of the anomalies is very small within the data. Patch-based techniques can incorporate any of the above methods [1, 2, 23, 24, 3, 4, 25, 26, 27], but aggregating patch-based results and metrics for meaningful and effective overall results is not always trivial [28].

3 Problems and Attempted Solutions

Problem	Attempted Solution	Outcome
volumes are 3D	3D models (varying slice thickness), work with slices and 2D models [29]	better signal-to-noise ratio with 2D slices
volumes are very large	work with patches [2]	better signal-to-noise ratio with patches
tumours are very rare	generative modeling [11, 15]	difficult due to low-data and data heterogeneity
tumours are very small	work with patches [1, 3], segmentation [20, 21, 22]	works better in low-data domains
varying bands of brightness in wbMRIs	contrast-limited adaptive histogram equalization [30]	better contrast and tumour visibility
some volumes are noisy	denoising techniques [31]	improved clarity and contrast
varying positions	registration [32]	difficult due to data heterogeneity
varying age and sex	conditioning on age and sex [33]	slower and more unstable training
varying size, shape, and location of tumours	augmentations [34], add synthetic tumours to training set [23, 24]	increased diversity of training data

Table 1: The problems encountered, the attempted solutions, and the outcomes of those attempts.

4 Dataset

Our dataset contains 675 wbMRI volumes (coronal STIR) from the imaging database of a children's hospital. On average, there are around 40 slices per volume, since the thickness of the slices varies across MRIs based on the MRI machine and settings. The number of slices ranges from 25 to 50 slices per volume. The dimensions of each slice also vary based on the MRI machine and settings in addition to the age, size, and height of the child, but on average, they are around 3000 pixels tall and 800 pixels wide.

Only 27 volumes contain tumours and there are a total of 60 tumours. Out of the approximately 27,437 slices in the dataset, are 120 slices that contain tumour sections, with the number of slices spanning a tumour ranging from 1-7 slices. The approximate diameter of each tumour ranges from 10 pixels to 100 pixels, which is very small compared to the size of a whole-body MRI volume.

After de-identification was used to remove all confidential information from the wbMRIs, the corresponding radiology reports, which indicated cancer locations within the body, were used by our radiologist fellows to perform manual annotations (i.e. segmentations) of tumours using a segmentation tool. These masks were used to train our tumour segmentation model.

We split the volumes into 4 folds for 4-fold cross-validation, with approximately the same number of slices with tumours in each, and also leave out a test set to evaluate performance.

4.1 Patches and Augmentations

As discussed before, due to the vast variation in tumours and wbMRIs across the dataset and the paucity of tumours within the dataset, we relied on patches and augmentations to train our model to find tumours efficiently and effectively. First, we find the number of tumours in each segmentation mask label along with their locations by finding the total number of contours. Then, for each tumour, we take a patch with the tumour at its centre and employ combinations of the following augmentations:

- Take multiple patches containing tumours with the centre uniformly randomly moved around by a few pixels in the x- and y- dimensions in a given slice to be able to find tumours that are not at the exact centre of a given test patch.
- Take multiple patches containing tumours with small zooms in or out of the slice to be able to find tumours occupying various proportions of a given test patch.
- Take multiple patches from anywhere within the volume to introduce patches with no tumours (i.e. negative samples) into the dataset.
- Take multiple patches from brighter parts of the volume (brain, bones, and parts of the abdomen) to avoid the model from learning all bright spots as tumours. This is done automatically by randomly taking patches of the volume above a certain average brightness threshold.
- Take multiple patches with the entire patch multiplied by a value smaller than and close to 1 for invariance in small changes to the brightness.
- Take multiple patches with the each pixel in a patch multiplied by a value smaller than and close to 1 for invariance to small amounts of noise.
- Take multiple patches from the same approximate location in the current volume in several different volumes that do not have a tumour in that location so that the model can learn to identify parts of the body with and without tumours more effectively.
- Take multiple patches without tumours and add synthetic tumours to them and blend them into the surrounding tissue. The size, shape, and brightness of these tumours is chosen randomly (see Section 4.2).

We applied these augmentations in conjunction with each other, rather than separately, to increase the variation in the location, shape, texture, and size (relative to the body and relative to the patch) of the tumour and allow the model to focus on learning to find tumours while remaining invariant to these factors. Note that the patch from the volume and its corresponding mask are taken from exactly the same location. All patches are 128 pixels by 128 pixels or resized to those dimensions in the case of the small zoom in and zoom out augmentations.

The patches are obtained from the cross-validation set and split by volume. We use 5707 patches with a 70%-30% training/validation split. 25% of the training and validation sets contain tumours.

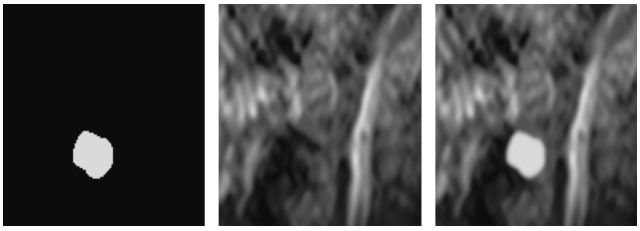

Figure 1: The generation and insertion of a synthetic tumour as described below.

4.2 Synthetic Tumour Generation

To increase the prevalence of positive cases (tumours) within the dataset of patches, we use the following process to generate patches with synthetic tumours (see Figure 1):

1. Create a tumour mask of random size by generating a random number of points, using Graham's scan [35] to find the convex hull, and interpolating smoothly between the points.
2. Choose a patch from within the volume without any tumours.

3. Choose a random brightness for the generated tumour and blend the generated tumour mask from step 1 onto the patch chosen in step 2 to match the texture.

This method allows us to generate synthetic tumours of varying shape, size, brightness, and location within the body to augment the training dataset.

5 Model and Loss Function

We use the U-Net model [20] along with a loss function that includes asymmetric unified focal loss [36], Dice loss [37], contour perimeter loss [38], and contour difference loss. The coefficients of each of these loss functions in the total patch loss (see Equation 1) are tunable hyperparameters.

$$\begin{aligned} Loss_{Patch} = \alpha * Loss_{AsymmetricUnifiedFocal} \\ + \beta * Loss_{Dice} \\ + \gamma * Loss_{ContourPerimeter} \\ + \delta * Loss_{ContourDifference} \end{aligned} \tag{1}$$

$Loss_{AsymmetricUnifiedFocal}$ is a combination of asymmetric focal Tversky loss and asymmetric focal loss, which enhance the hard class and suppress the easy class in segmentation tasks.

$Loss_{Dice}$ is used to better deal with the imbalance between the foreground and background pixels.

$Loss_{ContourPerimeter}$ and $Loss_{ContourDifference}$ are used to ensure that the model does not over-guess or under-guess the size of a tumour and that the segmentation is localized properly, respectively. These losses are listed in terms of their importance in the total loss and are weighted accordingly.

The number of patches, the batch size, the optimizer, the learning rate, the learning rate scheduler, and the proportions of augmentations are the other tunable hyperparameters.

6 Experiments

Model	Dice Score	TPR	FPR	TPR > 10%
U-Net w/ $Loss_{Dice}$	0.9097 / **0.8200**	0.9874 / 0.9391	0.0080 / **0.0096**	0.9926 / 0.9550
U-Net w/ $Loss_{Patch}$	0.8328 / 0.7644	0.9834 / 0.9457	0.0179 / 0.0139	0.9908 / 0.9651
U-Net w/ $Loss_{Patch}$ + Augmentations + Synthetic Tumours	0.8014 / 0.7577	0.9754 / **0.9527**	0.0167 / 0.0155	0.9858 / **0.9704**

Table 2: Average of the patch-based results across the folds for training / validation. TPR > 10% signifies the percent of patches that matched the predicted mask with the true mask by over 10% of the size of the true mask. True negative patches count towards this number.

We take the best trained model, for each fold, from Table 2, i.e. the U-Net model trained with $Loss_{Patch}$ + Augmentations + Synthetic Tumours, and use a sliding window approach, with 25% overlap, to get a prediction mask for each slice in every volume. The whole-body results on the cross-validation set for the volumes with tumours are as follows: 27/53 tumour detections in 16/21 volumes. For the test set, we have: 6/7 tumour detections in 5/6 volumes.

The false-positive rate in a given volume ranges from 0.5% to 2% of the pixels, but tumours, if they exist, account for approximately 0.01% to 0.0001% of a given volume, which means that there are 50-20,000 times more false-positive pixels than true-positive pixels. False positive pixels usually occur in the brighter parts of the body.

Although it is important for both the false-positive rate and the false-negative rate to be low and there is a trade-off in trying to minimize both, it is more important to not miss too many tumours (i.e. lowering the false-negative rate is a bit more crucial). However, if it is at the expense of a very high false positive rate, then there will be too many areas highlighted with high tumour probability, which would make it challenging to differentiate between the true positives and the false positives to find the actual tumours. It is also important to note that the Dice score is easily affected by the size of the tumours and it is therefore more insightful to consider a variety of metrics to evaluate patch-level performance. See Figure 2 to see examples of patch-level performance and Figure 3 to see examples of performance on entire slices.

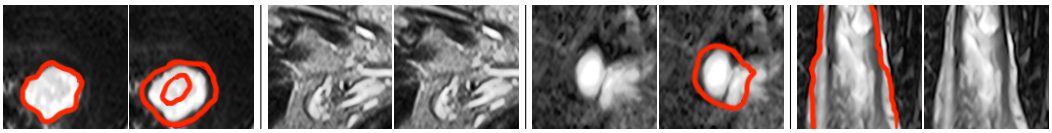

Figure 2: Examples of a 1. true positive, 2. true negative, 3. false positive, and 4. false negative when identifying a tumour (from left to right). Each pair of images contain the contours of the true and predicted masks (red outline).

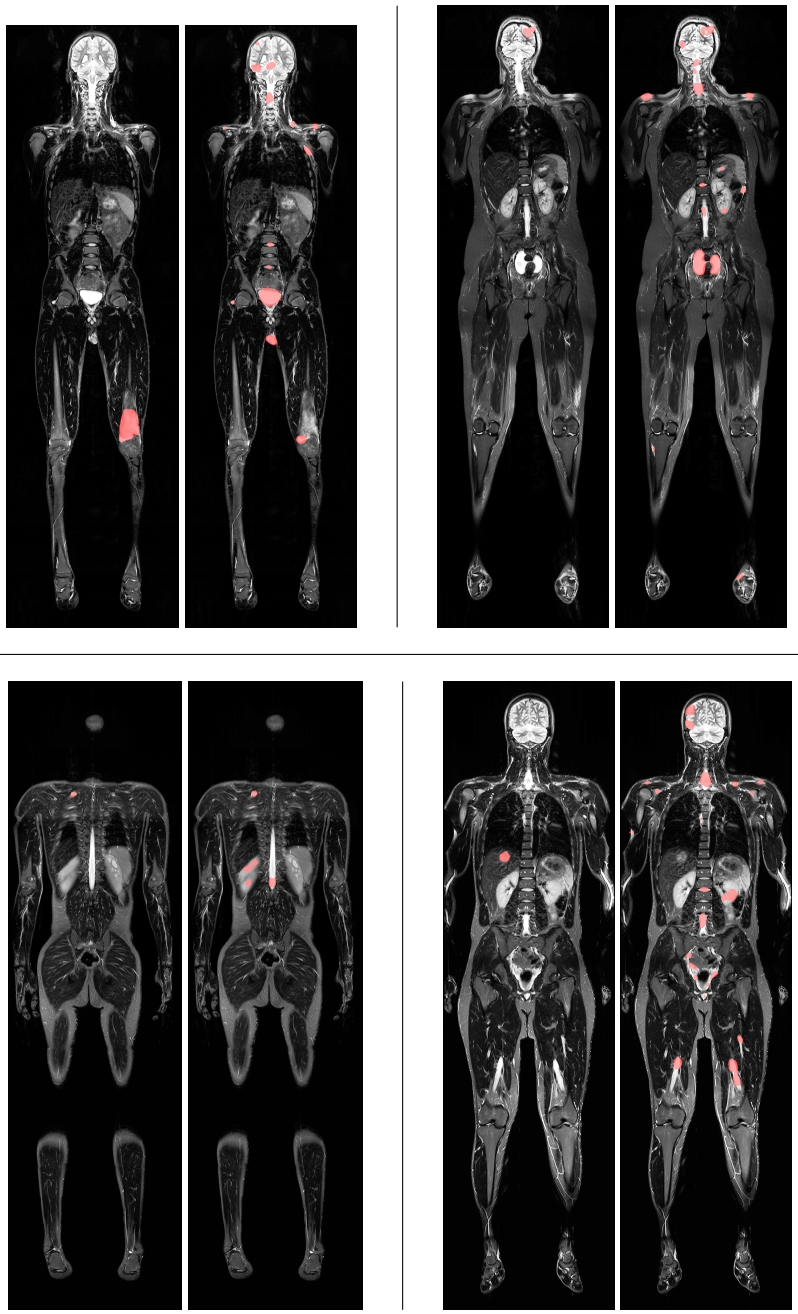

Figure 3: Four examples of whole-body MRI slices in pairs of true mask overlays and predicted mask overlays. Top left: part of the knee tumour is identified. Top right: entire brain tumour is identified. Bottom left: tumour above lung is identified. Bottom right: tumour in the liver is missed. False positives exist in every example, usually in the brighter parts of the image.

For each of the 120 tumour sections in the cross-validation set, we compare the average brightness and overall size of the tumour in Figure 4 when a tumour is detected or missed. Note that a tumour is classified as a "detect" when any part of the tumour is predicted and a tumour is classified as a "miss" when none of the tumour is predicted. There are no clear patterns, but we can notice that very large and very bright tumours are usually detected, whereas very small and very faint tumours are usually missed by our segmentation model. A total of 58/120 tumour sections are detected, which means that just more than half of the tumour sections are missed.

The discrepancy between the results in the 3rd row of Table 2 and Figure 4 suggest that strong performance at the patch-level does not necessarily translate to the whole-body-level due to the fact that we curate the dataset of patches, have a much higher imbalance at the whole-body-level, and may be unable to properly foresee the false-positive rate at the whole-body-level from only considering the patch-level performance.

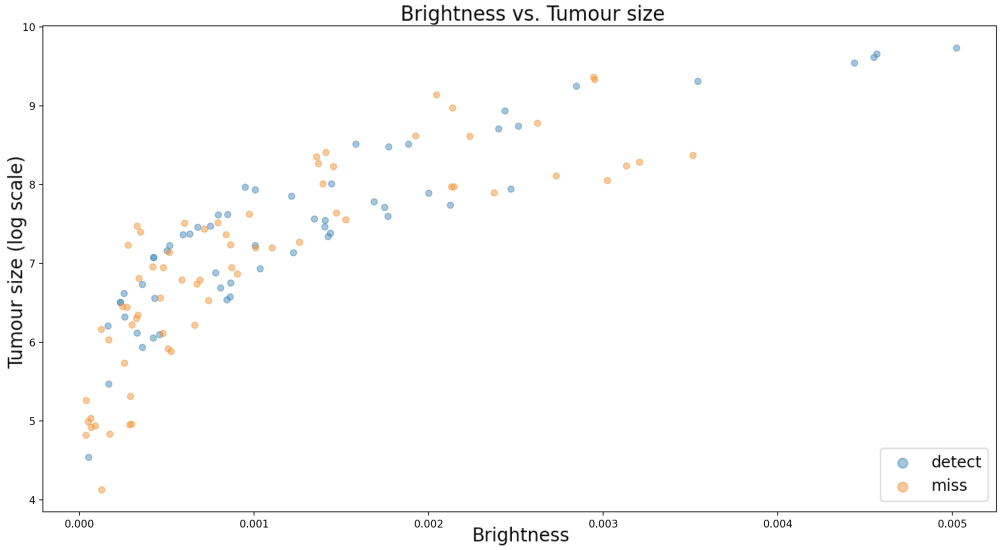

Figure 4: Average tumour brightness vs. tumour size (log scale) when a tumour is detected or missed.

For example, the following approaches improved patch-based results but worsened the whole-body-based results by either increasing the false-positive rate or the false-negative rate: more proportion of augmentations, more proportion of patches with synthetic tumours, more weighting in the loss function to the parts which deal with lowering the false-positive rate (i.e. asymmetric unified focal loss and Dice loss), and varying proportions of tumour augmentations as discussed in Section 4.1.

7 Discussion & Future Work

We employ many tools to make use of the small amount of positive cases and large amount of negative cases. We split the data into patches, use the U-Net segmentation model, select the appropriate proportions and types of patches, utilize a compound loss function consisting of losses dealing with each issue in the domain, augment large portions of the data, and add patches with synthetic tumours. Although each of these approaches consistently improved the results at the patch-level from the baseline, we noticed that the results at the whole-body-level did not see major improvements and, in some cases, worsened.

Our work highlights the need for future methods to follow through on finding a more holistic approach to consolidate strong patch-based results into consistently strong whole-image-based results. Similar results have been found in other domains utilizing patch-based learning such as for cancer detection in whole slide images [28]. This is because even if patch-based results seem promising, they may not be clinically relevant. Machine learning practitioners must continue to address the issues of data heterogeneity and low signal-to-noise ratio in the medical domain and report the appropriate user-relevant metrics.

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