An image analysis approach to MRI brain tumour grading

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Brain tumours are caused by abnormal and uncontrolled growth of cells inside the brain or spinal canal. They are the second cause of death related to Cancer in children and adults younger than 34 years [1]. The primary tumours are those that start in the brain and are categorised in four main types: Gliomas, Meningiomas, Pituitary adenomas and Nerve sheath tumours. The most popular grading system for tumours is that suggested by the World Health Organization (WHO). Regarding to the WHO grading system, the tumours are graded from I to IV, corresponding to least advanced to the most advanced diseases, respectively.

Utilising computer-aided procedures for medical diagnosis and treatment is a growing field of research. Among these procedures, Medical Image Analysis plays a substantial role, especially in cancer management [2]. The image processing applications in Cancer management include prediction, screening, biopsy guidance for detection, staging, prognosis, therapy planning, and therapy response [3].

Depending on the imaging modality, images provide quantification measures alongside the visualisation of the target tissue. Characteristics obtained from images such as location, size of the tumour, and imaging parameters [4] can be used for screening tasks in brain cancer. Whole-body Magnetic Resonance (MR) imaging is another way of screening for Cancer. In this method, metastases that are caused by a tumour; are monitored in other organs of the body. Research shows that MR imaging provides more accurate results for detection of metastases in comparison to other modalities [5].

Using diffusion weighted imaging is popular for investigating tumour response and allows early predictions of tumour presence [6]. However, conventional MR imaging can also be used for prediction tasks in brain or other types of cancers. Kawahara et al. [7] investigated four different factors of T1 protocols and suggested that by combining them and using multivariate regression analysis is helpful for prediction of high-grade meningioma.

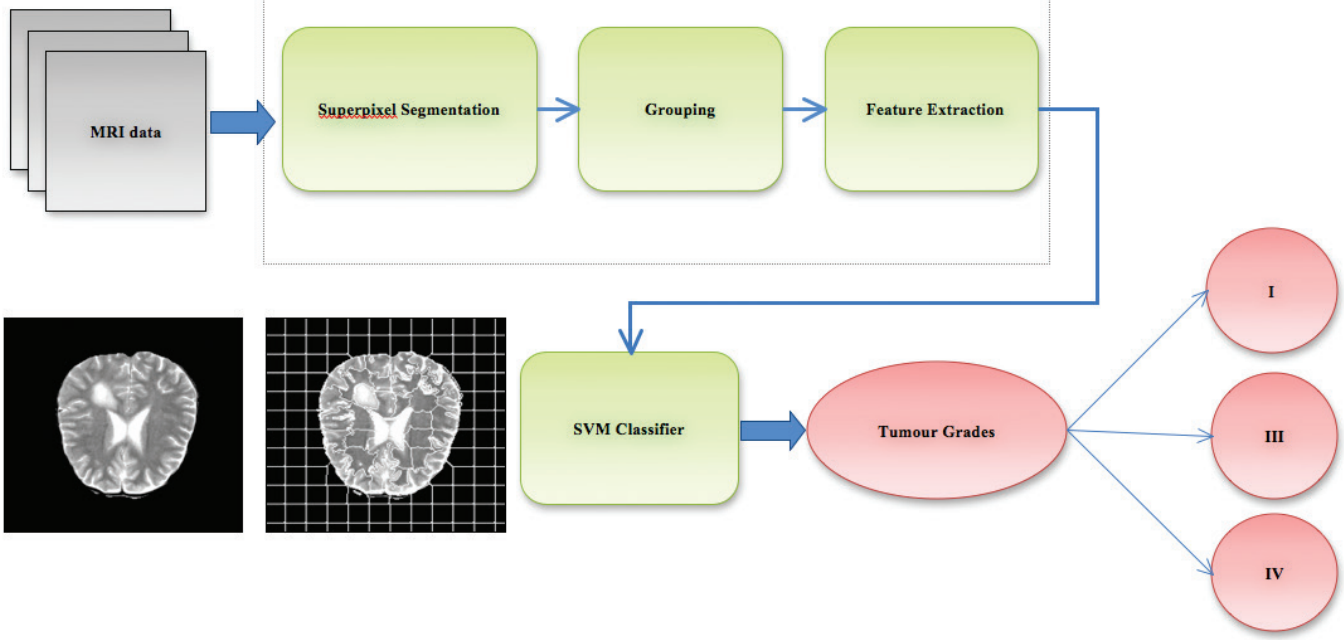
Medical Image Analysis research methods commonly consist of several parts, which use different algorithms in a sequence or a pipeline. Some pre-processing stages maybe used to prepare the data for optimum results. These algorithms consist of segmentation, feature extraction and classification. Segmentation is based on visual characteristics of the images, which are related to their grey-levels. Features are statistical measurements and information that can be extracted from a selected part of the image. Classification is the process of categorisation the data based on their features which is a necessary stage for grading the tumours. These methods can be implemented independently as the main or as an auxiliary stage alongside with the main part of the algorithm.

Image processing and pattern recognition algorithms are widely used for analysis and interpretation of medical images. Feature extraction is the most important and impartible element of classification and pattern recognition tasks. In the case of medical images, such as MRI, the reduction of dimensionality is of high importance. MRI images are three-dimensional volumetric data acquired with different protocols, which lead to extraction of high dimensional information in the form of statistical features. Classification of high dimensional data is based on these extracted features.

Georgias et al. [8] utilised a pattern recognition system based on support vector machine classifiers and combination of features extracted form MRI images and spectroscopy ratios. Their method efficiently discriminates between meningioma and metastatic brain tumours. Zacharaki et al. [9] performed a comprehensive assessment of pattern recognition methods on detection of different types of brain tumours and grading gliomas based on WHO grading system. They used a set of different image features including: intensity, shape, statistical characteristics and texture. Regarding to the high dimensionality of the feature space, they used feature selection methods to find an optimum feature subset.

Angelini et al. [10] proposed a differential analysis system to measure the growth of low-grade glioma in MRI brain images. Joshi et al. [11] developed a system for detection of Astrocytoma cancer tumours and classify them based on artificial neural network. Georgiadis et al. [12] proposed a method to classify primary and metastatic tumours, which originated outside the brain. Soltaninejad et al. [13] proposed a framework for classifying different tumour grades exploring information from several MRI acquisition protocols, see figures 1 and 2 for the algorithmic layout and initial results.

Figure 1. The flowchart of proposed method.



MRI Brain Tumour Imaging and Analysis

MRI is the most commonly used imaging modality for brain tumour assessment [14], as it provides efficient evaluation of tumour analysis and the acquisition is non-invasive [15].

Segmentation in medical images means partitioning the pixels to detect and separate the target area usually a tissue or a lesion from the background and healthy tissues. In some research fields, segmentation of a specific tissue or tumour is the main purpose. In others, segmentation is an intermediate stage for further analysis such as classification or other measurements. For the case of brain tumours, it is a difficult task regarding to the characteristics of the tumour in the MR images [15]. The first stage in most medical image processing research is pre-processing. The most popular pre-processing method is noise suppression or correcting for non-uniformities. There are several algorithms proposed for this task that beside their benefits, they may have negative effects on further processing stage [16]. Before any analysis on a specific target in the image, it is necessary to segment that from other parts in the image. Image segmentation algorithms use edge, region or intensity properties of the target tissue in the image to separate them from the background [17]. The aim of edge-based segmentation methods is to find the boundary of two adjacent regions that have different characteristics. One of the most popular algorithms for detection of tumour edges in MRI images

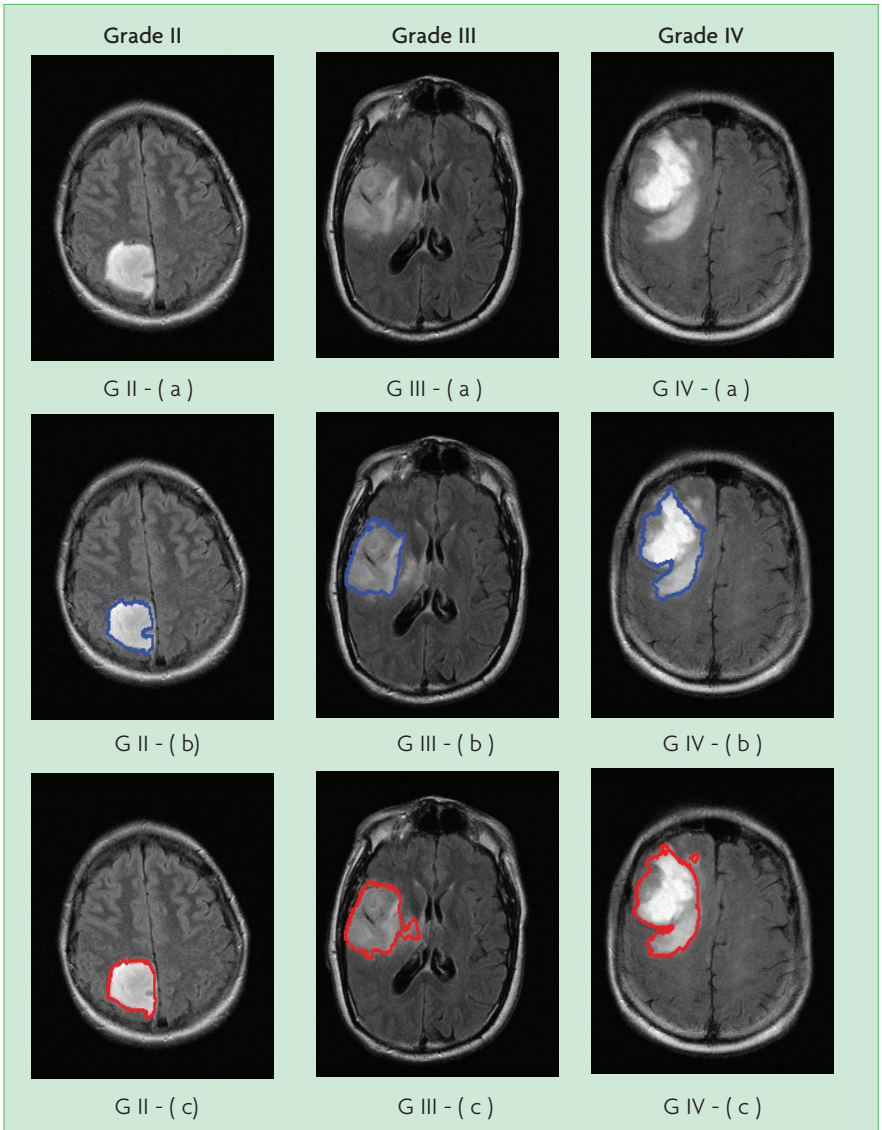


Figure 2: Examples of Grade II, III, and IV brain oedemas: a) original MRI slice, b) superpixel segmentation, c) manual segmentation.

is using level-sets [18] and/or combining it with classification or clustering methods [19]. In our work [13], we use the properties from sub-regions of the image. These sub-regions are grouped together based on their similar characteristics and their spatial adjacency. The image is segmented to small partitions using a linear iterative clustering superpixel (SLIC) algorithm [20]. Superpixels are groups of pixels with similar features.

Feature extraction

Feature extraction is a step used for both segmentation and classification of tissues in medical images. Since the tumours have different types and grades and there are different acquisition protocols, the tumour region in the image may have different properties. So, a wide range of feature types can be used in image analysis of brain tumours [15]. Intensity features are most popular in this field. The idea is that tumours have different intensity in comparison to other healthy tissues. Several statistical measures can be calculated from the pixels of the target area in the image. The other common features are based on textural patterns [22], as different tumour regions have specific textures. Fractal-based features are also used for brain tumour segmentation and detection [23], as well as context features for segmentation in MRI brain images [24].

The features may be extracted from a single MRI acquisition protocol [25] (i.e. FLAIR, T1-weighted, T2-weighted, etc.) or using different protocols together [26]. Even combinations of features from different modalities are investigated [27]. However, such strategy dramatically increases the number of features acquired, and to overcome this, the employment of feature selection methods for choosing an efficient set of them with the highest classification accuracy [28] should be considered.

Classification for grading

Classification in machine learning means finding a model, based in a set of training data, in order to categorise a general set of data. Classification algorithms can be used in supervised segmentation of MRI images [29]. Automatic brain tumour segmentation methods often use this type of segmentation [30]. Some further analysis tasks for medical images are also involved with classification. One of them is grading the tumours based on their type, which is also called tumour grading. The data for training the classification model are the features that are extracted from the images. Each feature vector has a label corresponding to the tumour type. The aim of classification is to find the class labels (i.e. tumour types) for the new images. Several classification methods are used for this purpose. A popular classification method in many medical applications is Support Vector Machine (SVM) that is used for brain tumour classification [9]. This method is suitable for two classes and can be extended for multiclass cases. In [31] a method is suggested based on combination of Neural Networks and Principal Component Analysis (PCA) for reducing the feature space and providing a more robust classifier. In [13] we investigated the application of a linear support vector machine classifier using datasets from different MRI imaging protocols in order to differentiate tumour grades II, III and IV. The assumption to use several protocols rather than a single approach is to obtain more information for training the classification system. Another issue we investigated is using multiple superpixel features from these protocols to assess their efficiency for classification. By increasing the feature space, it seems that advanced classification techniques should be utilised to improve the grading task.

Discussion and outlook

Image analysis and computer vision techniques are widely used for detection and grading the tumours in medical images. Due to developments in imaging and processing techniques, using the state-of-the-art pattern recognition and computer vision in advanced imaging modalities with multi-modal approach attracts the most attention in today's research.

The variety of issues and complexity of brain in MRI images had made it a challenging task to perform automated image analysis. The current brain image analysis methods, due to their long computational time, are mostly confined in research-focused institutions, and are not applicable for generic clinical usage. Most of them are for specific imaging protocols that target specific lesion types, and usually are tested on a relative small group of data.

Any proposed automated MRI brain tumour segmentation/grading system should consider the real-world issues and be acceptable by the physicians for everyday use. Data that is used for training such systems should come from multi-centre collaborations and try to cover as many different imaging protocols, tumour types, and grades, as possible. The provided solutions besides being efficient in terms of speed, accuracy, and robustness, they also should be comprehensive and standardised. The challenge remains for state-of-the-art computational techniques to bridge the gap between research-oriented implementations and clinical routine applications.

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REFERENCES

1. Cha S. *Perfusion MR imaging of brain tumors.* Topics in Magnetic Resonance Imaging 2004:15(5);279-89.
2. Atri M. *New technologies and directed agents for applications of cancer imaging.* Journal of Clinical Oncology 2006:24(20);3299-308.
3. Fass L. *Imaging and cancer: a review.* Molecular Oncology 2008:2(2);115-52.
4. Rodjan F, de Graaf P, Brisse HJ, et al. *Trilateral retinoblastoma: neuroimaging characteristics and value of routine brain screening on admission.* Journal of Neuro-Oncology 2012:109(3);535-44.
5. Lauenstein TC, Goehde SC, Herborn CU, et al. *Whole-Body MR Imaging: Evaluation of Patients for Metastases 1.* Radiology 2004:233(1);139-48.
6. Heijmen L, Verstappen MC, ter Voert EE, Punt CJ, Oyen WJ, de Geus-Oei LF, Hermans JJ, Heerschap A, van Laarhoven HW. *Tumour response prediction by diffusion-weighted MR imaging: Ready for clinical use?* Critical reviews in oncology/hematology 2012:83(2);194-207.
7. Hiroyuki Nakamura, Jun-ichi Kuratsu, Kawahara Y, Nakada M, Hayashi Y, Kai Y, Hayashi Y, Uchiyama N, Nakamura H, Kuratsu J, Hamada JI. *Prediction of high-grade meningioma by preoperative MRI assessment.* Journal of Neuro-Oncology 2012:108(1);147-52.
8. Georgiadis P, Kostopoulos S, Cavouras D, Glotsos D, Kalatzis I, Sifaki K, Malamas M, Solomou E, Nikiforidis G. *Quantitative combination of volumetric MR imaging and MR spectroscopy data for the discrimination of meningiomas from metastatic brain tumors by means of pattern recognition.* Magnetic Resonance Imaging 2011:29(4);525-35.
9. Zacharaki EI, Wang S, Chawla S, Soo Yoo D, Wolf R, Melhem ER, Davatzikos C. *Classification of brain tumor type and grade using MRI texture and shape in a machine learning scheme.* Magnetic Resonance in Medicine, 2009:62(6);1609-18.
10. Angelini ED, Delon J, Bah AB, Capelle L, Mandonnet E. *Differential MRI analysis for quantification of low grade glioma growth.* Medical Image Analysis 2012:16(1);114-26.
11. Joshi DM, Rana NK, Misra VM. *Classification of brain cancer using artificial neural network.* In 2010 International Conference on Electronic Computer Technology (ICECT), 2010, (pp. 112-116). IEEE.
12. Georgiadis P, Cavouras D, Kalatzis I, Daskalakis A, Kagadis GC, Sifaki K, Malamas M, Nikiforidis G, Solomou E. *Improving brain tumor characterization on MRI by probabilistic neural networks and non-linear transformation of textural features.* Computer methods and Programs in Biomedicine 2008:89(1);24-32.

13. Soltaninejad M, Ye X, Yang G, Allinson N, Lambrou T. *Brain Tumour Grading in Different MRI Protocols using SVM on Statistical Features.* Medical Image Understanding and Analysis 2014:259-64.
14. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Chang SM. *Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group.* Journal of Clinical Oncology 2010:28(11);1963-72.
15. Bauer S, Wiest R, Nolte LP, Reyes M. *A survey of MRI-based medical image analysis for brain tumor studies.* Physics in medicine and biology 2013:58(13);R97.
16. Diaz I, Boulanger P, Greiner R, Murtha A. *A critical review of the effects of de-noising algorithms on MRI brain tumor segmentation.* In Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE 2011; (3934-7). IEEE.
17. Gonzalez RC, Woods RE. Digital image processing, 2002.
18. Ho S, Bullitt E, Gerig G. *Level-set evolution with region competition: automatic 3-D segmentation of brain tumors.* In Pattern Recognition, 2002. Proceedings. 16th International Conference on 2002;Vol. 1, 532-5. IEEE.
19. Satheesh S, Prasad KVSVR, Reddy KJ. *Brain Tumor Extraction from T1-Weighted MRI using Co-clustering and Level Set Methods.* International Journal of Image Processing (IJIP) 2013:7(2);219.
20. Achanta R, Shaji A, Smith K, Lucchi A, Fua P, Susstrunk S. *SLIC superpixels compared to state-of-the-art superpixel methods.* IEEE Transactions on Pattern Analysis and Machine Intelligence 2012:34(11);2274-82.
21. Rexilius J, Hahn HK, Klein J, Lentschig MG, Peitgen HO. *Multispectral brain tumor segmentation based on histogram model adaptation.* In Medical Imaging 2007;65140V-65140V). International Society for Optics and Photonics.
22. Kassner A, Thornhill RE. *Texture analysis: a review of neurologic MR imaging applications.* American Journal of Neuroradiology 2010;31(5);809-16.
23. Iftekharuddin KM, Zheng J, Islam MA, Ogg RJ. *Fractal-based brain tumor detection in multimodal MRI.* Applied Mathematics and Computation 2009:207(1);23-41.
24. Tu Z, Bai X. *Auto-context and its application to high-level vision tasks and 3d brain image segmentation.* Pattern Analysis and Machine Intelligence, IEEE Transactions on, 2010:32(10);1744-57.
25. Jack CR, O'Brien PC, Rettman DW, Shiung MM, Xu Y, Muthupillai R, Erickson BJ. *FLAIR histogram segmentation for measurement of leukoaraiosis volume.* Journal of Magnetic Resonance Imaging 2001:14(6);668-76.
26. Valdés Hernández MDC, Gallacher PJ, Bastin ME, Royle NA, Maniega SM, Deary IJ, Wardlaw JM. *Automatic segmentation of brain white matter and white matter lesions in normal aging: comparison of five multispectral techniques.* Magnetic resonance imaging 2012:30(2);222-9.
27. Ahmed S, Iftekharuddin KM, Vossough A. *Efficacy of texture, shape, and intensity feature fusion for posterior-fossa tumor segmentation in MRI.* Information Technology in Biomedicine, IEEE Transactions on 2011:15(2);206-13.
28. Simonetti AW, Melssen WJ, Edelenyi FSD, van Asten JJ, Heerschap A, Buydens L. *Combination of featureâreduced MR spectroscopic and MR imaging data for improved brain tumor classification.* NMR in Biomedicine 2005:18(1);34-43.
29. van Opbroek A, Ikram MA, Vernooij MW, de Bruijne M. *Supervised image segmentation across scanner protocols: A transfer learning approach.* In Machine Learning in Medical Imaging 2012;160-7 Springer Berlin Heidelberg.
30. Clark MC, Hall LO, Goldgof DB, Velthuizen R, Murtagh FR, Silbiger MS. *Automatic tumor segmentation using knowledge-based techniques.* Medical Imaging, IEEE Transactions on 1998:17(2);187-201.
31. Zhang Y, Dong Z, Wu L, Wang S. *A hybrid method for MRI brain image classification.* Expert Systems with Applications 2011:38(8);10049-53.

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Prognostic Value of Tumour-Infiltrating Lymphocytes in Triple-Negative Breast Cancers From Two Phase III Randomised Adjuvant Breast Cancer Trials: ECOG 2197 and ECOG 1199

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Purpose: Recent studies suggest that tumour-infiltrating lymphocytes (TILs) are associated with disease-free (DFS) and overall survival (OS) in operable triple-negative breast cancer (TNBC). We sought to validate the prognostic impact of TILs in primary TNBCs in 2 adjuvant phase III trials conducted by the Eastern Cooperative Oncology Group (ECOG). **Patients and Methods:** Full-face hematoxylin and eosin–stained sections of 506 tumours from ECOG trials E2197 and E1199 were measured for density of TILs in intraepithelial (iTILs) and stromal compartments (sTILs). Patient cases of TNBC from E2197 and E1199 were randomly selected, based on availability of sections. For the primary end-point of DFS, association with TIL scores was determined by fitting proportional hazards models stratified on study. Secondary end-points were OS and distant recurrence-free interval (DRFI). Reporting recommendations for tumour marker prognostic studies criteria were followed and all analyses were prespecified. **Results:** The majority of the 481 cancers assessed had TILs (sTILs, 80%; iTILs, 15%). With a median follow-up of 10.6 years, higher sTIL scores correlated with better prognosis; for every 10% increase in sTILs, a 14% reduction of risk of recurrence or death (P=0.02), an 18% reduction of risk of distant recurrence (P=0.04), and a 19% reduction of risk of death (P=0.01) were estimated. Multivariable analysis confirmed sTILs are an independent prognostic marker of DFS, DRFI and OS. **Conclusions:** In two national randomised clinical trials using contemporary adjuvant chemotherapy, we have confirmed that stromal lymphocytic infiltration constitutes a robust prognostic factor in TNBCs. Studies assessing outcomes and therapeutic efficacies should consider stratification for this parameter.

Reviewer's opinion: This study addressed the contribution of the immune system to outcome in the least favourable subtype of early stage breast cancer:- a highly topical issue, particularly in view of the emerging efficacy of immune-based therapeutics in many cancers, including PD-1/2 and PD1-2 ligand targeting, Sipuleucel-T (prostate cancer) and ipilimumab (melanoma). Previous studies suggested the predictive and prognostic impact of tumour-infiltrating-lymphocyte (TIL) density in breast cancer in neo-adjuvant and adjuvant settings. The strength of this study is the inclusion of a large number of patients (n=481), a subset with assessable tumour were representative of larger trial population, use of a previously validated simple and reproducible assessment of TIL density with good concordance between two blinded pathologists, and long-term (>10 years) thorough clinical follow-up. The key finding was that stromal TIL density positively correlated with disease-free survival, distant recurrence-free interval and overall survival in both uni- and multi-variate analyses (not including tumour grade). It is notable that the density of intra-epithelial TILs (i.e. those in direct contact with tumour cell islets) was not correlated with clinical outcomes, and was generally low. Therefore further characterisation of the phenotype and function of the stromal TILs is important. It is unexpected that so simple a measure of immune infiltration (CD3 T-cell density) correlates well with outcome, given the diversity of leucocytes present in tumours. Future challenges will be to standardise and possibly automate assessment of TIL density in routine diagnostic histopathology laboratories, and to determine how to combine conventional cytotoxic chemotherapy, targeted therapies directed against defective DNA damage repair (i.e PARP inhibitors) and nascent immunotherapies in this difficult-to-treat and undoubtedly immunogenic cancer. It remains unclear how an estimate of TIL density on a pathology report would change clinical decision-making, although patients with no TIL infiltrate might be considered for trials involving immune-stimulating treatments. – AR