Figure 1

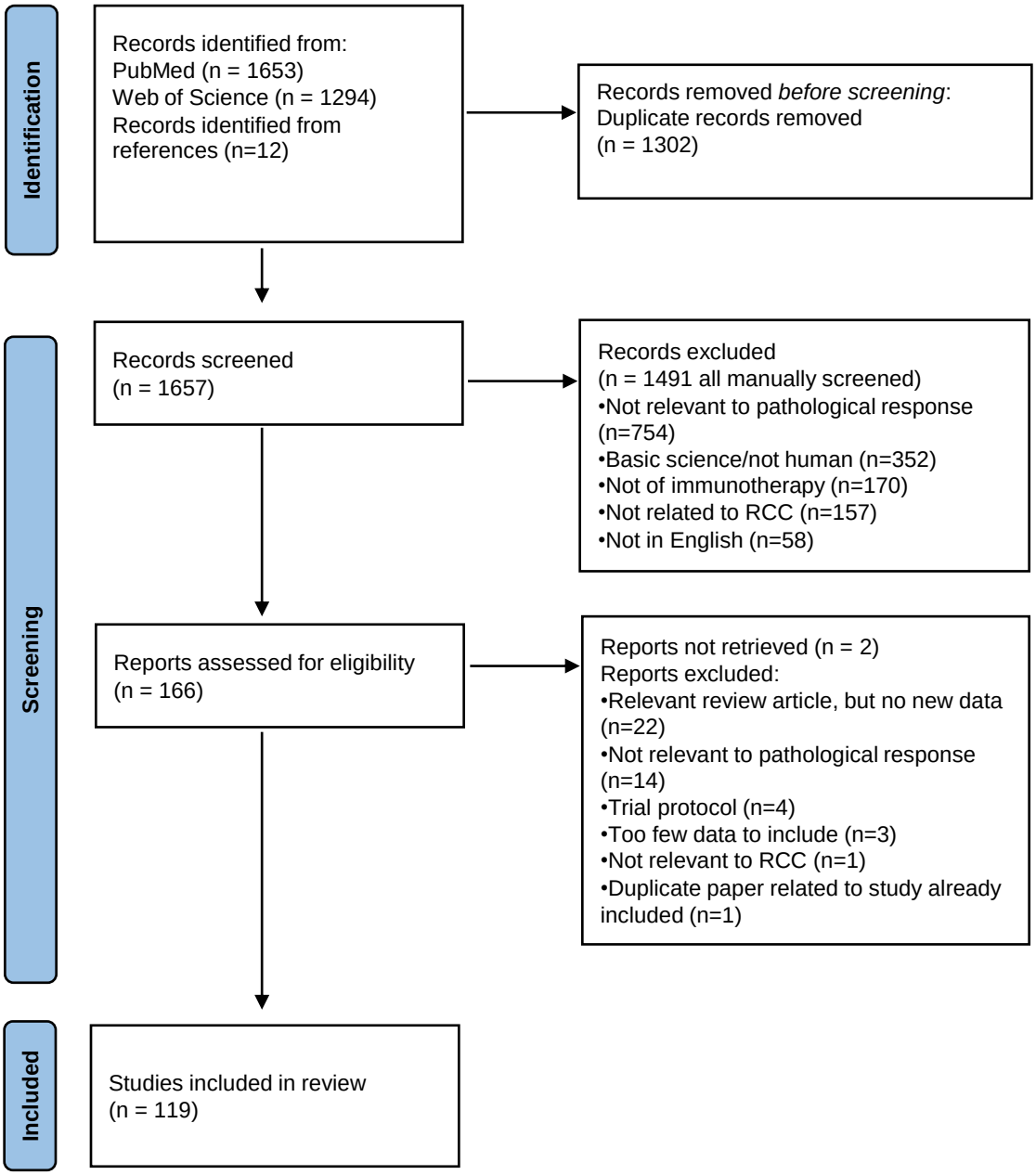


Figure 1: PRISMA flow diagram summarising the systematic review process

Figure 2

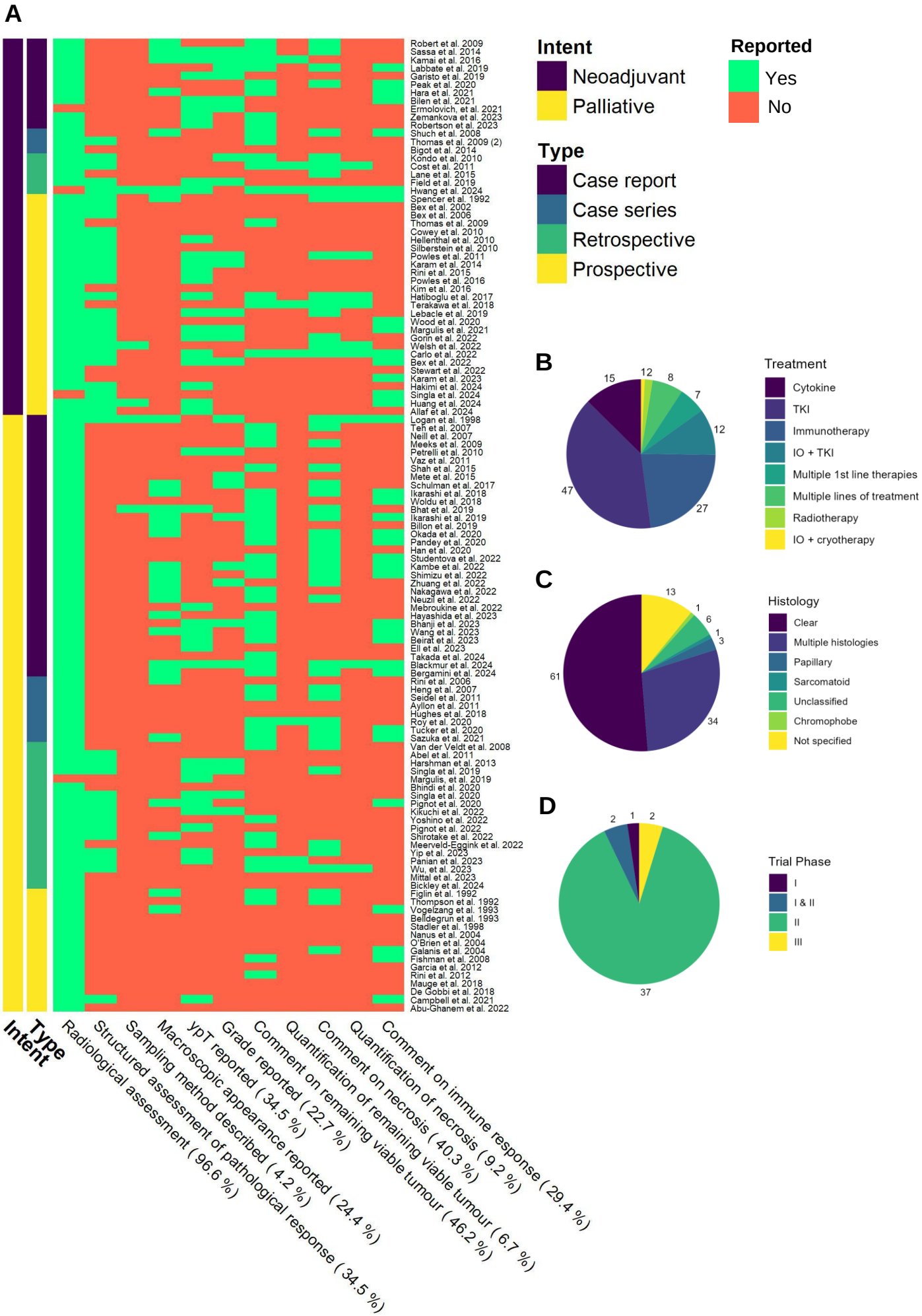

A
Intent
Neoadjuvant
Palliative
Reported
Yes
No
Type
Case report
Case series
Retrospective
Prospective
Robert et al. 2009
Sassa et al. 2014
Kamai et al. 2016
Labbate et al. 2019
Garisto et al. 2019
Peak et al. 2020
Hara et al. 2021
Bilen et al. 2021
Ermolovich, et al. 2021
Zemankova et al. 2023
Robertson et al. 2023
Shuch et al. 2008
Thomas et al. 2009 (2)
Bigot et al. 2014
Kondo et al. 2010
Cost et al. 2011
Lane et al. 2015
Field et al. 2019
Hwang et al. 2024
Spencer et al. 1992
Bex et al. 2002
Bex et al. 2006
Thomas et al. 2009
Cowey et al. 2010
Hellenthal et al. 2010
Silberstein et al. 2010
Powles et al. 2011
Karam et al. 2014
Rini et al. 2015
Powles et al. 2016
Kim et al. 2016
Hatiboglu et al. 2017
Terakawa et al. 2018
Lebacle et al. 2019
Wood et al. 2020
Margulis et al. 2021
Gorin et al. 2022
Welsh et al. 2022
Carlo et al. 2022
Bex et al. 2022
Stewart et al. 2022
Karam et al. 2023
Hakimi et al. 2024
Singla et al. 2024
Huang et al. 2024
Allaf et al. 2024
Logan et al. 1998
Teh et al. 2007
Neill et al. 2007
Meeks et al. 2009
Petrelli et al. 2010
Vaz et al. 2011
Shah et al. 2015
Mete et al. 2015
Schulman et al. 2017
Ikarashi et al. 2018
Woldu et al. 2018
Bhat et al. 2019
Ikarashi et al. 2019
Billon et al. 2019
Okada et al. 2020
Pandey et al. 2020
Han et al. 2020
Studentova et al. 2022
Kambe et al. 2022
Shimizu et al. 2022
Zhuang et al. 2022
Nakagawa et al. 2022
Neuzil et al. 2022
Mebroukine et al. 2022
Hayashida et al. 2023
Bhanji et al. 2023
Wang et al. 2023
Beirat et al. 2023
Ell et al. 2023
Takada et al. 2024
Blackmur et al. 2024
Bergamini et al. 2024
Rini et al. 2006
Heng et al. 2007
Seidel et al. 2011
Ayllon et al. 2011
Hughes et al. 2018
Roy et al. 2020
Tucker et al. 2020
Sazuka et al. 2021
Van der Veldt et al. 2008
Abel et al. 2011
Harshman et al. 2013
Singla et al. 2019
Margulis, et al. 2019
Bhindi et al. 2020
Singla et al. 2020
Pignot et al. 2020
Kikuchi et al. 2022
Yoshino et al. 2022
Pignot et al. 2022
Shirotake et al. 2022
Meerveld-Eggink et al. 2022
Yip et al. 2023
Panian et al. 2023
Wu, et al. 2023
Mittal et al. 2023
Bickley et al. 2024
Figlin et al. 1992
Thompson et al. 1992
Vogelzang et al. 1993
Belldegrun et al. 1993
Stadler et al. 1998
Nanus et al. 2004
O'Brien et al. 2004
Galanis et al. 2004
Fishman et al. 2008
Garcia et al. 2012
Rini et al. 2012
Mauge et al. 2018
De Gobbi et al. 2018
Campbell et al. 2021
Abu-Ghanem et al. 2022
Intent
Type
Radiological assessment of pathological response (34.5 %)
Structured assessment of pathological response (96.6 %)
Sampling method described (4.2 %)
Macroscopic appearance reported (24.4 %)
ypT reported (34.5 %)
Grade reported (22.7 %)
Comment on remaining viable tumour (46.2 %)
Quantification of remaining viable tumour (6.7 %)
Comment on necrosis (40.3 %)
Quantification of necrosis (9.2 %)
Comment on immune response (29.4 %)
B
15
12
8
7
12
27
47
Treatment
Cytokine
TKI
Immunotherapy
IO + TKI
Multiple 1st line therapies
Multiple lines of treatment
Radiotherapy
IO + cryotherapy
C
13
1
6
1
3
34
61
Histology
Clear
Multiple histologies
Papillary
Sarcomatoid
Unclassified
Chromophobe
Not specified
D
2
1
2
37
Trial Phase
I
I & II
II
III

Figure 2: Systematic review results.

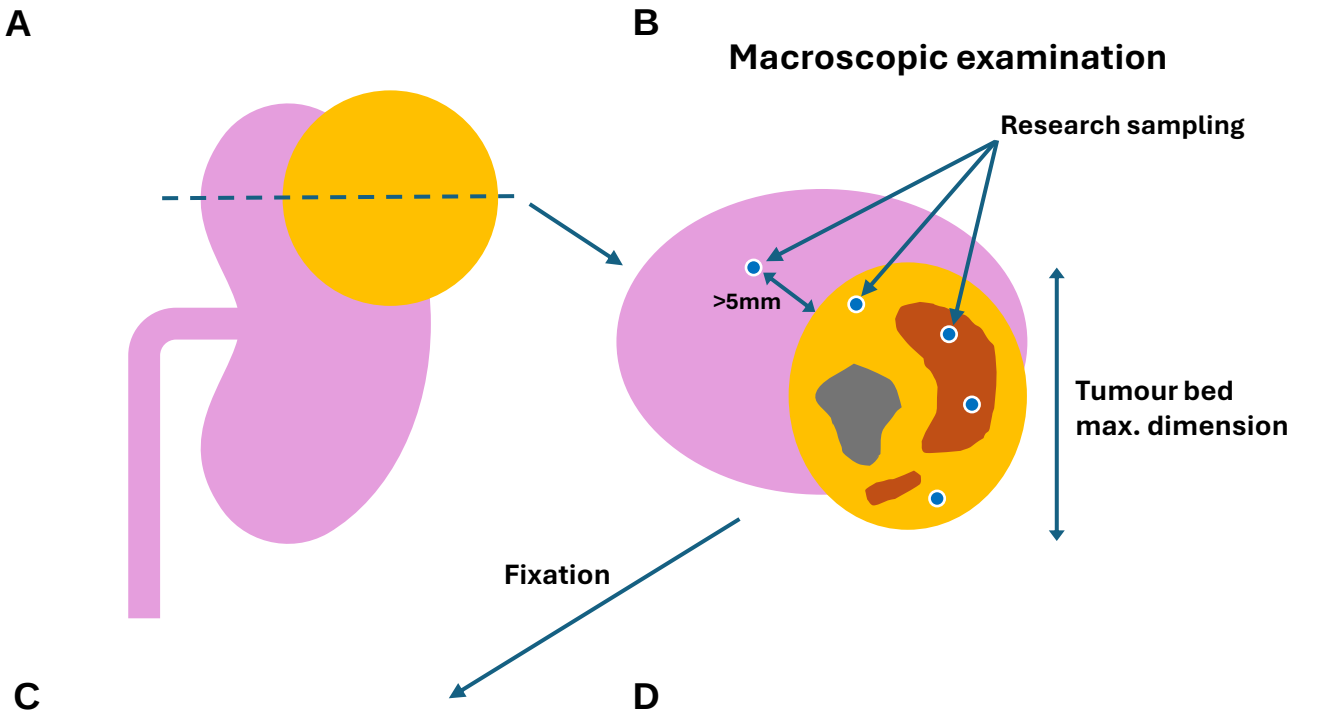
A. Heatmap summarising the findings of the systematic review. Studies are grouped according to treatment intent and study type. Percentages of studies fulfilling each criteria are indicated at the bottom of each column.

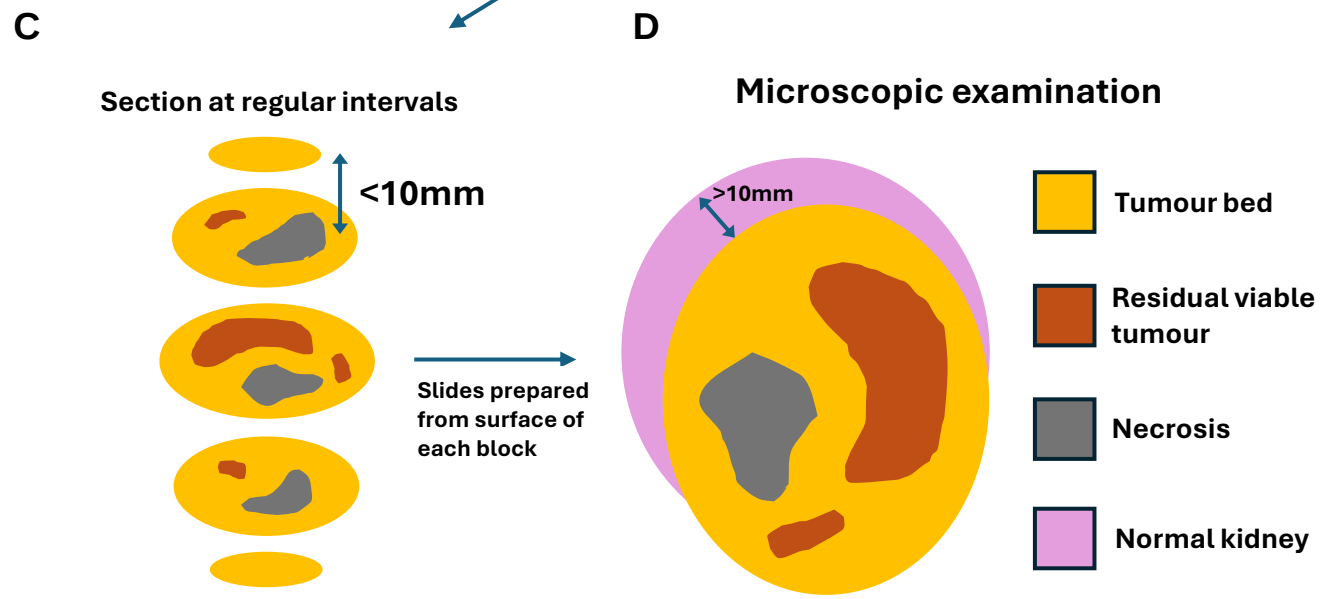
B. Proportions of studies using different anticancer treatments. IO = immunotherapy, TKI = VEGFR directed tyrosine kinase inhibitor. "Multiple 1st line treatments" indicates all the patients received 1st line therapy, but different therapies were included.

C. Proportions of studies including each histological type. "Multiple histologies" indicates more than one histological subtype was included in the study.

D. Summary of trial phase for prospective studies

Figure 3





$$\left[\frac{\text{Residual viable tumour area}}{\text{Total tumour bed area}}\right] \text{ X } 100 = \% \text{ residual viable tumour}$$

Percentage Residual Viable Tumour	Pathological Response Classification
>50%	Non response
<50%	Partial response
<10%	Major response
0%	Complete response

Figure 3: Sampling strategy and microscopic assessment of pathological response.

A. Tumour is divided along maximal dimension of tumour bed.

B. Macroscopic examination of the cut surface, including recording of the maximal dimension of the tumour bed. The cut surface should be photographed for reference. Fresh research samples may be taken at this point. The locations of research samples should be mapped using a systematic method. Normal kidney samples should be taken at least 5mm away from the tumour margin.

C. After fixation, the tumour is sectioned at intervals of <10mm. 10mm of adjacent normal tissue should be included.

D. Microscopic slides are assessed to estimate the percentage residual viable tumour and necrosis. When calculating the percentage residual viable tumour, the total tumour bed area should be used. i.e. the area inclusive of any viable tumour and necrotic areas. Standard pathological assessments should also be conducted including histological subtype, grade and ypT staging.

Figure 4

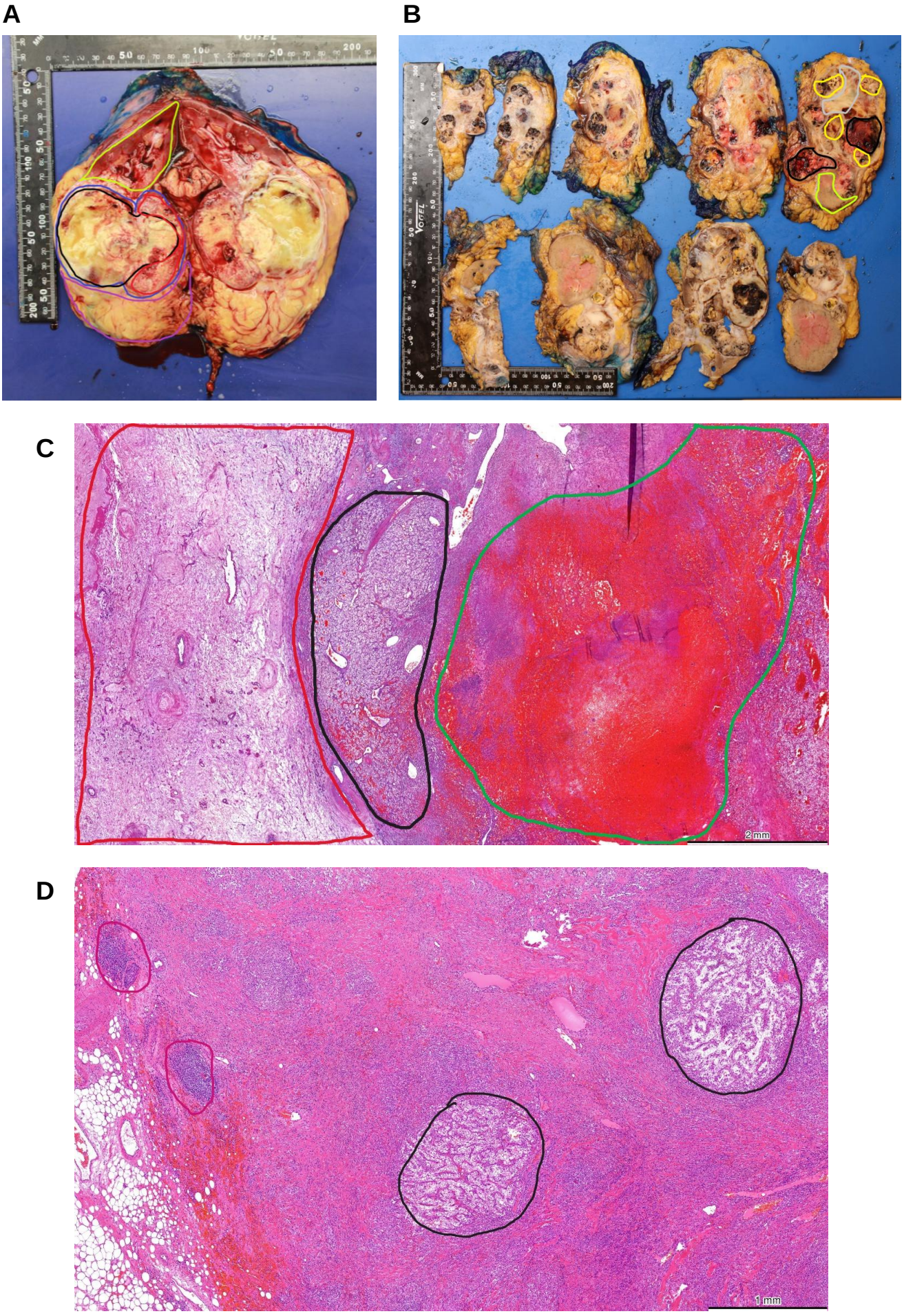


Figure 4. Macroscopic and microscopic assessment of response to neoadjuvant therapy.

A. Nephrectomy specimen after treatment with ipilimumab and nivolumab. Total tumour bed marked in blue, area with necrosis/fibrosis in black, viable tumor in red. Normal kidney parenchyma in green, renal adipose tissue in purple. Macroscopic response was estimated: viable tumour area (17)/ total tumour bed area (100) x 100 = 17%, documented as 20% (to nearest 10% interval).

B. Nephrectomy specimen after treatment with ipilimumab and nivolumab. Tumour shows characteristic heterogeneity of clear cell renal cell carcinoma with yellow/brown solid areas (yellow lines), haemorrhagic areas (black lines), sclerotic areas (grey line). Normal kidney parenchyma in green. No response to neo-adjuvant immunotherapy was observed.

C. Classic clear cell renal cell carcinoma, with viable clear cell morphology (black line), sclerotic acellular areas (red line) and haemorrhagic areas (green line). The sclerotic area should not be confused with response to therapy.

D. Clear cell carcinoma with response to neo-adjuvant therapy. In the background a fibrotic area with diffuse infiltration of lymphoid cells. Viable tumour areas in black, to the left (red lines) tertiary lymphoid structures. Note the patchy distribution of small areas with viable tumour. Since this cannot be observed grossly, extensive sampling is advised. Residual viable tumour was assessed at <10% of the tumour bed area: major pathological response.