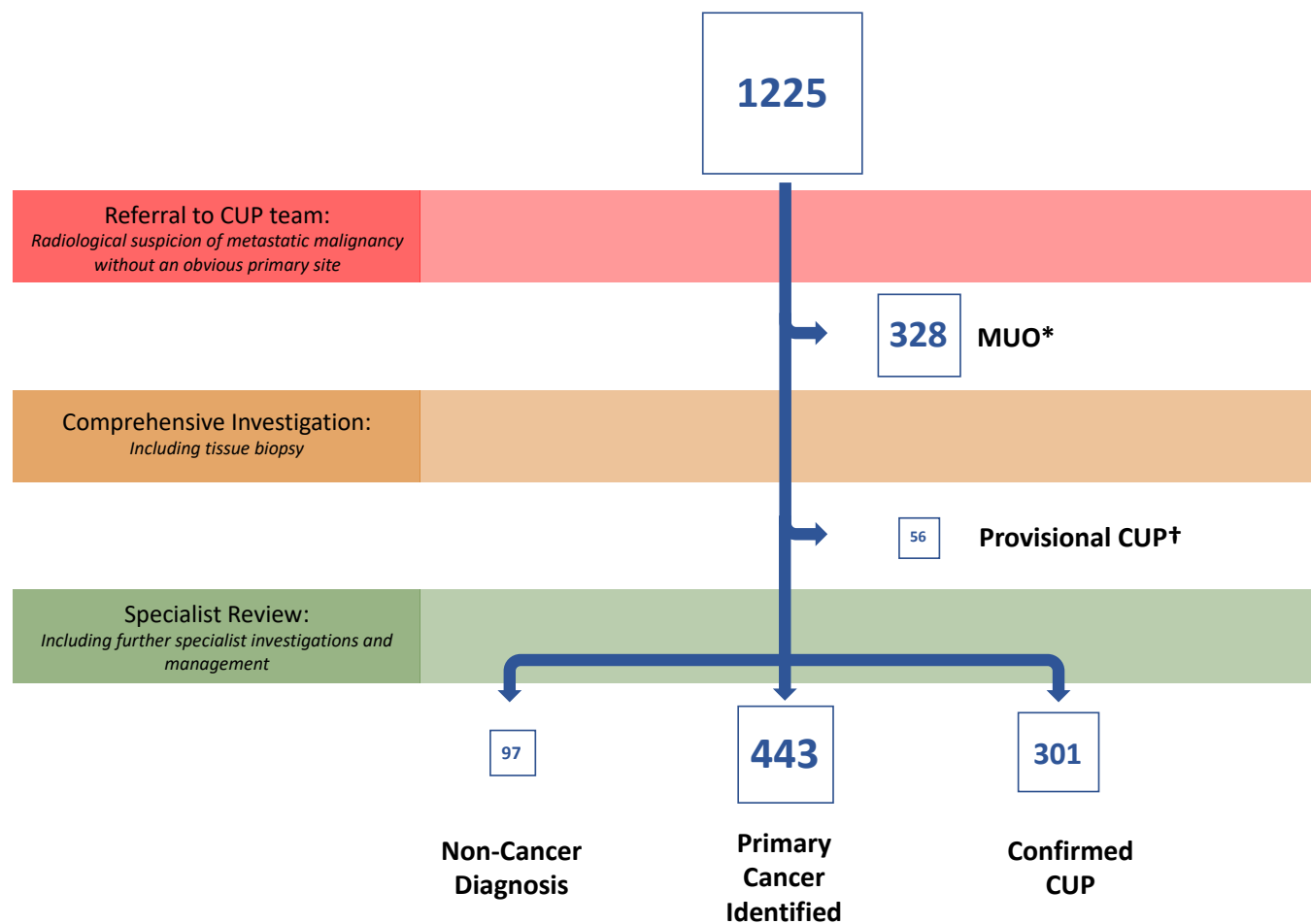
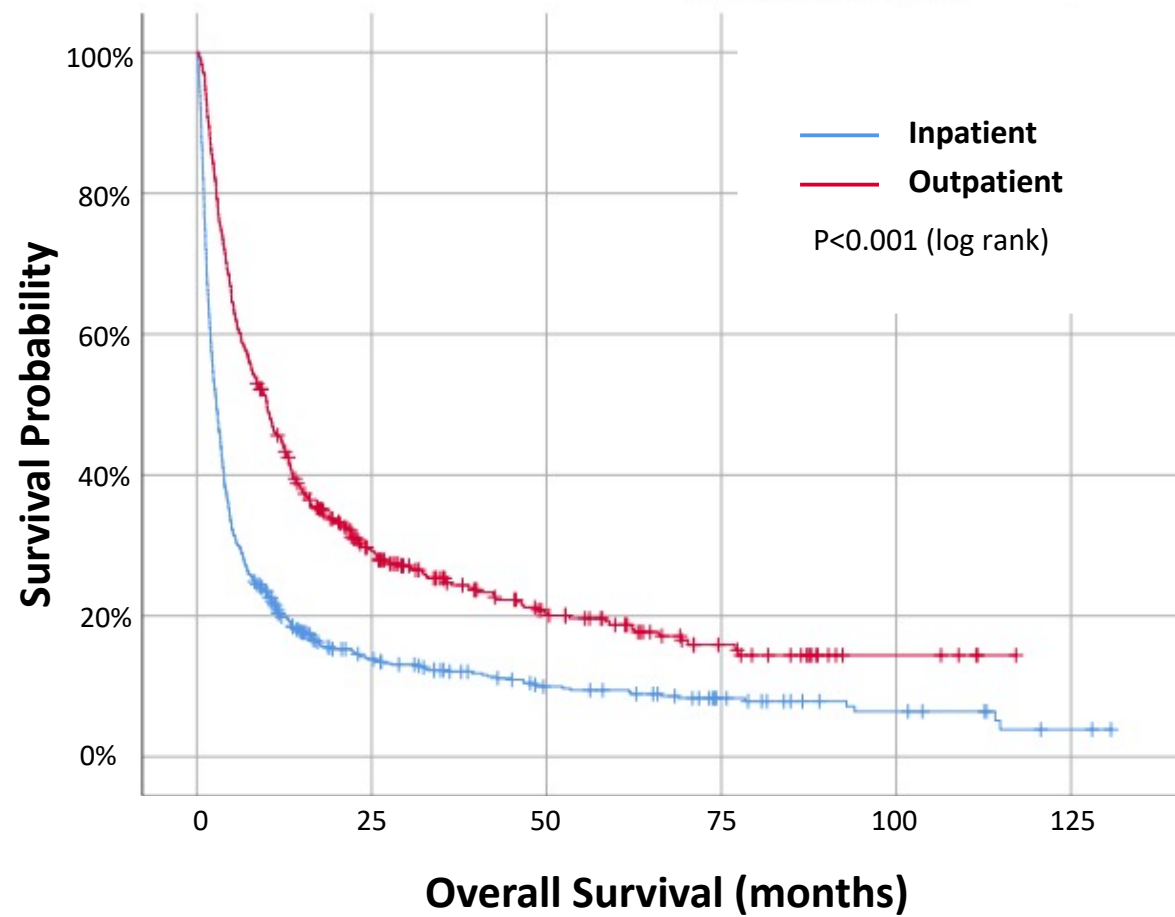


Supplementary Figure 1: Pathway and diagnostic subgroups of patients referred to the ECC Cancer of Unknown Primary Team over 10 years

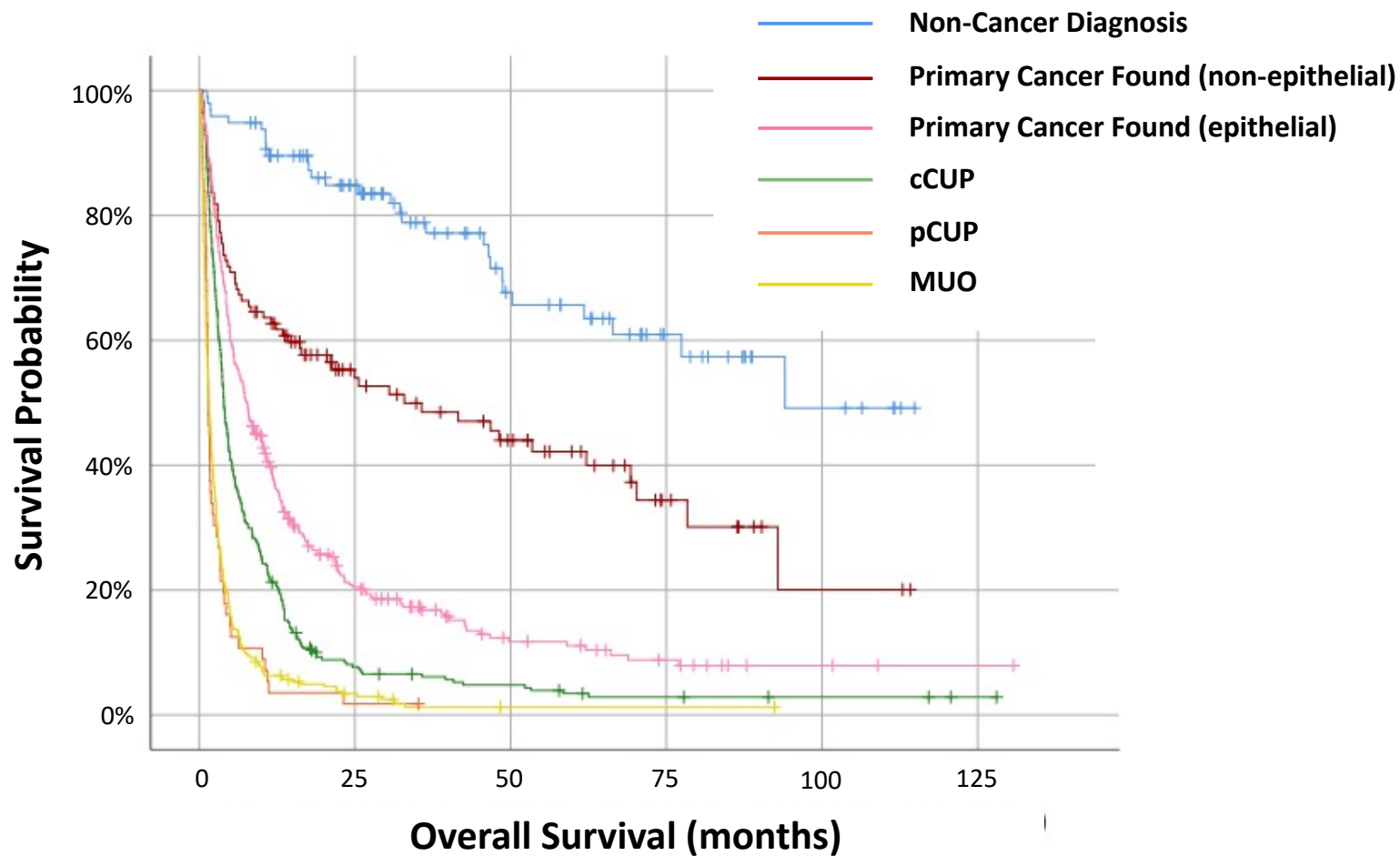


MUO* - comprehensive investigation, including biopsy, not clinically appropriate; pCUP † - comprehensive investigation, including biopsy, complete but patient not fit to be seen in specialist CUP clinic

Supplementary Figure 2: Kaplan Meier curves examining survival of patients referred to the ECC CUP team by route of referral

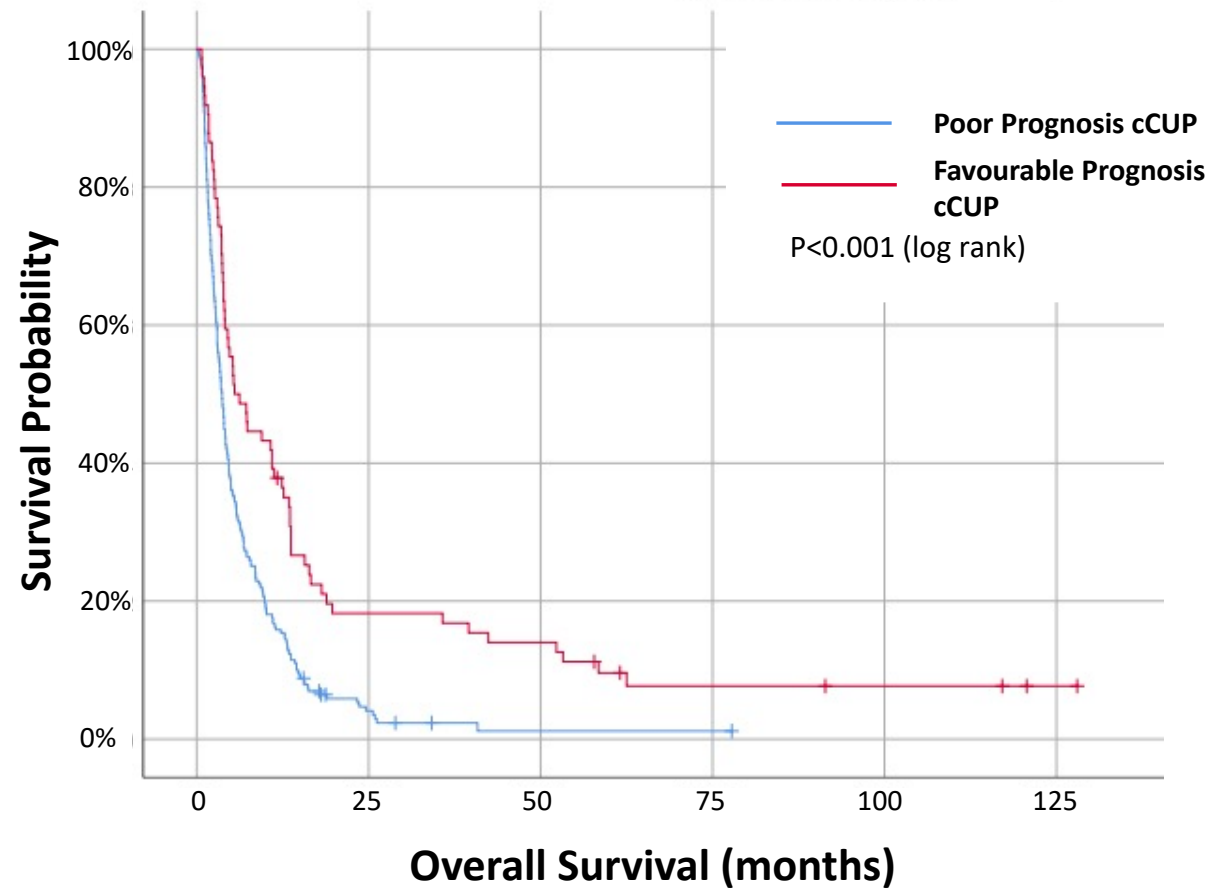


Supplementary Figure 3: Kaplan Meier curves examining survival for all diagnostic groups, sub-dividing Primary Cancer Found into epithelial and non-epithelial* malignancies

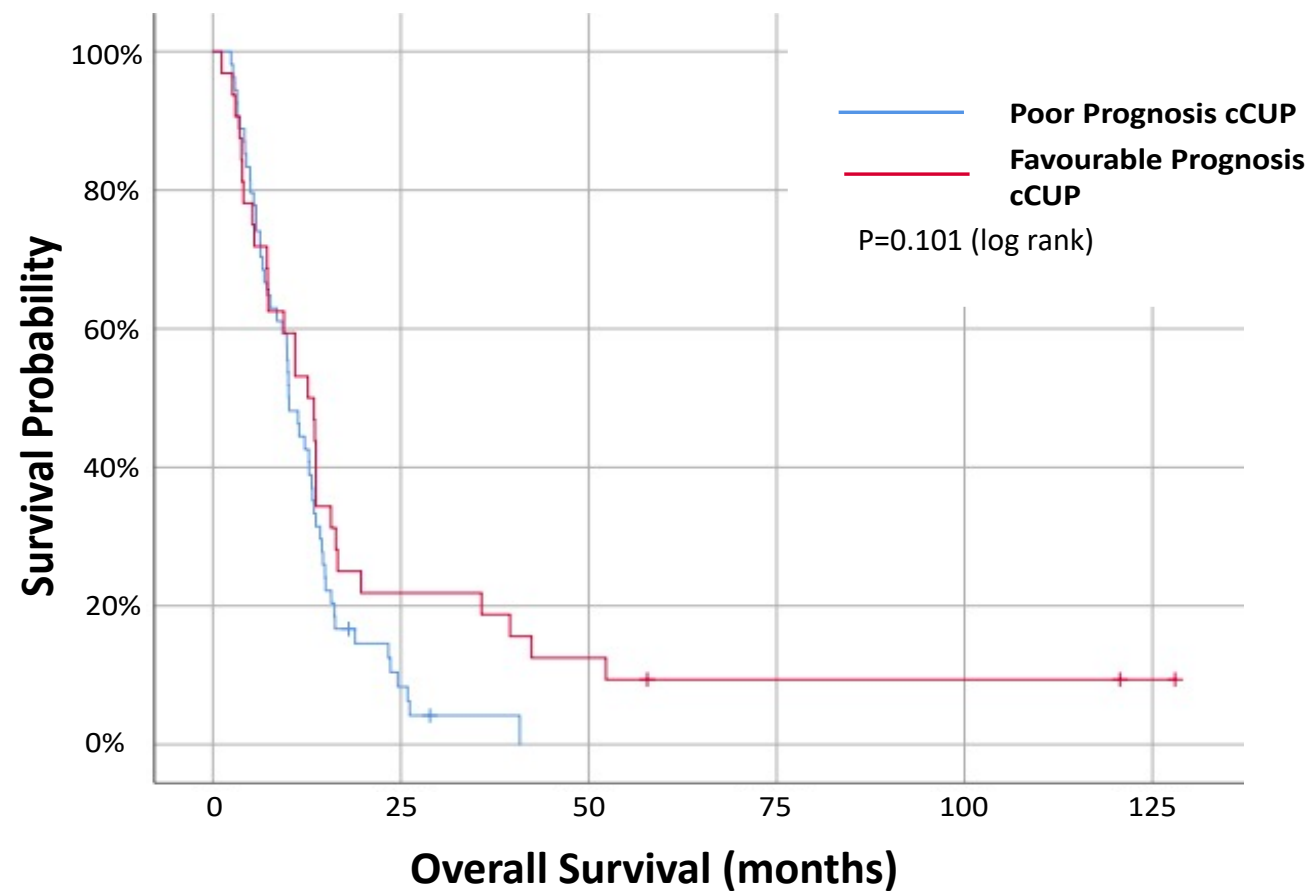


Non-epithelial malignancies * - lymphoma, myeloma, sarcoma, melanoma

Supplementary Figure 4: Kaplan Meier curves examining survival of patients with cCUP by clinicopathological prognostic group



Supplementary Figure 5: Kaplan Meier curves examining survival of patients with cCUP treated with systemic anticancer therapy by clinicopathological prognostic group



Supplementary Table 1: Reasons patients with a final diagnosis of MUO did not undergo comprehensive investigations and associated median survival

Reason for not undergoing comprehensive investigation	n (%)	Survival (Months) median (IQR)
Frailty*	262 (80)	1.4 (0.7-2.9)
Patient wishes	39 (12)	2.3 (1.2-3.9)
Biopsy attempt unsuccessful	17 (5)	3.5 (1.6-6.4)
No accessible lesion	10 (3)	4.7 (2.9-10.4)

Frailty* was broadly defined as poor performance status and/or clinical unsuitability for invasive investigation or systemic anticancer therapy

Supplementary Table 2: Source of referrals to the ECC CUP by route of referral

			All	Non-Cancer Diagnosis	Primary Cancer Identified	Confirmed CUP	Provisional CUP	MUO
			1225	97	443	301	56	328
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Source of Referral	Medicine	All	714 (58)	59 (61)	237 (53)	153 (51)	31 (55)	234 (71)
		I/P	555 (45)	37 (38)	177 (40)	106 (35)	27 (48)	208 (63)
		O/P	159 (13)	22 (23)	60 (13)	47 (16)	4 (7)	26 (8)
	Surgery	ALL	241 (20)	12 (12)	89 (20)	74 (25)	19 (34)	47 (14)
		I/P	172 (14)	8 (8)	56 (13)	52 (17)	17 (30)	39 (12)
		O/P	67 (5)	4 (4)	31 (7)	22 (8)	2 (4)	8 (2)
	General Practice	ALL	132 (11)	17 (18)	68 (16)	16 (5)	3 (5)	28 (9)
		I/P	n/a	n/a	n/a	n/a	n/a	n/a
		O/P	132 (11)	17 (18)	68 (16)	16 (5)	3 (5)	28 (9)
	Other Cancer MDT	ALL	122 (10)	7 (7)	41 (9)	57 (19)	3 (5)	14 (4)
		I/P	10 (1)	n/a	5 (1)	4 (1)	0 (0)	1 (0)
		O/P	112 (9)	7 (7)	36 (8)	53 (18)	3 (5)	13 (4)
	Radiology	ALL	16 (1)	2 (2)	8 (2)	1 (0)	0 (0)	5 (2)
		I/P	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	n/a
		O/P	15 (1)	2 (2)	7 (2)	1 (0)	0 (0)	5 (2)

I/P – referred as inpatient; O/P – referred as outpatient

Supplementary Table 3: Presenting complaints prompting initial radiological investigations in patients referred to the ECC CUP team

		All	Non-Cancer Diagnosis	Primary Cancer Identified	Confirmed CUP	Provisional CUP	MUO
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Selected Presenting Complaints	Pain	650 (53)	41 (42)	247 (56)	182 (60)	32 (57)	148 (45)
	Weight Loss	509 (42)	23 (24)	162 (37)	127 (42)	26 (46)	171 (52)
	Altered Bowel Habit	151 (12)	4 (4)	51 (12)	46 (15)	10 (18)	40 (12)
	Palpable Lump/Mass	117 (10)	3 (3)	15 (11)	42 (14)	4 (7)	18 (5)
	Hypercalcaemia	51 (4)	2 (2)	14 (3)	14 (5)	3 (5)	18 (5)
	Spinal Cord Compression	55 (4)	1 (1)	27 (6)	17 (6)	0 (0)	10 (3)
	Other Neurological Symptoms*	118 (10)	9 (9)	61 (14)	11 (4)	0 (0)	37 (11)
	Pathological Fracture	16 (1)	2 (2)	6 (1)	3 (1)	1 (2)	4 (1)

Other neurological symptoms* - included limb weakness, sensory disturbance, visual disturbance, seizures

Supplementary Table 4: Sites of disease on initial radiological investigations in patients referred to the ECC CUP team

		All	Non-Cancer Diagnosis	Primary Cancer Identified	Confirmed CUP	Provisional CUP	MUO
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Patients	<i>Patients</i>	1225	97	443	301	56	328
	Adrenal	94 (8)	2 (2)	43 (10)	21 (7)	4 (7)	24 (7)
	Bone	360 (29)	36 (37)	148 (33)	78 (26)	10 (18)	88 (27)
	Brain	114 (9)	12 (12)	44 (10)	13 (4)	0 (0)	45 (14)
	Liver	501 (41)	16 (16)	147 (33)	124 (41)	22 (39)	192 (59)
	Lung	372 (30)	20 (21)	126 (28)	89 (30)	14 (25)	123 (38)
	Peritoneal	224 (18)	7 (7)	56 (13)	72 (24)	22 (39)	67 (20)
	Thoracic LN	206 (17)	5 (5)	72 (16)	75 (25)	9 (16)	45 (14)
	Cervical/Axillary LN	98 (8)	5 (5)	39 (9)	39 (13)	4 (7)	11 (3)
	Abdominal/Pelvic LN	343 (28)	10 (10)	133 (31)	101 (34)	13 (23)	86 (26)
Single Site of Disease	<i>Patients</i>	469	70	169	100	26	104
	Adrenal	3 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)
	Bone	126 (27)	27 (39)	57 (33)	17 (17)	4 (16)	21 (20)
	Brain	48 (10)	6 (9)	15 (9)	5 (5)	0 (0)	22 (21)
	Liver	98 (21)	11 (16)	33 (20)	15 (15)	6 (24)	33 (32)
	Lung	20 (4)	8 (11)	3 (1)	2 (2)	1 (4)	6 (6)
	Peritoneal	63 (13)	4 (6)	13 (8)	27 (27)	7 (28)	12 (12)
	Thoracic LN	13 (3)	2 (3)	4 (2)	7 (7)	0 (0)	0 (0)
	Cervical/Axillary LN	18 (4)	0 (0)	10 (6)	5 (5)	2 (8)	1 (1)
	Abdominal/Pelvic LN	33 (7)	4 (6)	11 (7)	13 (13)	2 (8)	3 (3)

Single Lesion	<i>Patients</i>	<i>91</i>	<i>22</i>	<i>32</i>	<i>14</i>	<i>1</i>	<i>21</i>
	Adrenal	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	Bone	33 (32)	13 (59)	9 (29)	4 (29)	0 (0)	7 (33)
	Brain	15 (16)	3 (14)	5 (16)	1 (7)	0 (0)	6 (29)
	Liver	10 (10)	3 (14)	4 (13)	0 (0)	1 (100)	2 (10)
	Lung	1 (1)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
	Peritoneal	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)
	Thoracic LN	1 (1)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)
	Cervical/Axillary LN	4 (4)	0 (0)	3 (9)	0 (0)	0 (0)	1 (5)
	Abdominal/Pelvic LN	2 (2)	0 (0)	1 (3)	1 (7)	0 (0)	0 (0)

Includes sites seen in >5% of all patients.

LN – lymph nodes.