**Remote Ischemic Preconditioning versus sham-control for prevention of anastomotic leakage after resection for Esophageal cancer (RIPE Trial): a pilot randomized controlled, triple-blinded monocenter trial (DRKS00018934)**

Study results are not yet published. However, we expect publication by 31/12/2023.

|  |  |  |  |
| --- | --- | --- | --- |
|  | RIPC (n= 28) | Sham (n= 27) | Overall Cohort(n= 55) |
| **Age** [years] | 61.5 ±9.05 | 64.7 ±8.76 | 63.1 ±8.97 |
| **Gender** (male:female) | 25:3 (89%:11%) | 21:6 (78%:22%) | 46:9 (84%:16%) |
| **BMI** [kg/m²] | 25.96 ±4.81 | 27.15 ±3.94 | 26.54 ±4.40 |
| **Preoperative serum albumin** [g/l] | 38.0 (25-42) | 38.6 (27-44) | 38.0 (25-44) |
| **ASA** |  |  |  |
| I | 2 (7%) | 0 (0%) | 2 (4%) |
| II | 16 (57%) | 20 (74%) | 36 (65%) |
| III | 10 (36%) | 7 (26%) | 17 (31%) |
| **Diabetes mellitus** |  |  |  |
| not insulin-dependent | 3 (11%) | 2 (7%) | 5 (9%) |
| insulin dependent | 0 (0%) | 3 (11%) | 3 (5%) |
| **Arterial hypertension** | 12 (43%) | 20 (74%) | 32 (58%) |
| **Nicotine abuse** | 15 (54%) | 16 (59%) | 31 (56%) |
| pack years | 40 (20-120) | 40 (2-71) | 38,8 (2-120) |
| **Alcohol abuse** | 7 (25%) | 0 (0%) | 7 (13%) |
| **Neoadjuvant therapy** |  |  |  |
| chemotherapy | 15 (54%) | 18 (67%) | 33 (60%) |
| chemoradiation | 7 (25%) | 5 (19%) | 12 (22%) |
| **Tumor histology** |  |  |  |
| adenocarcinoma | 25 (89%) | 26 (96%) | 51 (97%) |
| squamous cell carcinoma | 3 (11%) | 1(4%) | 4 (3%) |
| **Tumor location** |  |  |  |
| cervical | 1 (4%) | 0 (0%) | 1 (2%) |
| mid thoracic | 5 (18%) | 5 (19%) | 10 (18%) |
| lower thoracic | 11 (39%) | 5 (19%) | 16 (29%) |
| esophagogastric junction | 11 (39%) | 17 (63%) | 28 (51%) |
| **TNM classification** |  |  |  |
| pT category |  |  |  |
| T0 | 10 (36%) | 8 (30%) | 18 (33%) |
| T1a,b | 8 (29%) | 4 (15%) | 12 (22%) |
| T2 | 4 (14%) | 5 (19%) | 9 (16%) |
| T3 | 6 (21%) | 10 (37%) | 16 (29%) |
| pN category |  |  |  |
| N0 | 23 (82%) | 14 (52%) | 37 (67%) |
| N1 | 2 (7%) | 8 (30%) | 10 (18%) |
| N2 | 2 (7%) | 4 (15%) | 6 (11%) |
| N3 | 1 (4%) | 1 (4%) | 2 (4%) |
| Grading |  |  |  |
| G1 | 1 (4%) | 2 (7%) | 3 (5%) |
| G2 | 11 (39%) | 11 (41%) | 22 (40%) |
| G3 | 16 (57%) | 14 (52%) | 30 (55%) |
| resection status |  |  |  |
| R0 | 27 (96%) | 24 (89%) | 51 (93%) |
| R1 | 1 (4%) | 3 (11%) | 4 (7%) |
| M category |  |  |  |
| M0 | 27 (96%) | 25 (93%) | 52 (95%) |
| M1 | 1 (4%) | 2 (7%) | 3 (5%) |
| **UICC stage** |  |  |  |
| 0 | 11 (40%) | 7 (26%) | 18 (33%) |
| IA/B | 9 (32%) | 3 (11%) | 12 (22%) |
| IIA/B | 1 (4%) | 5 (19%) | 6 (11%) |
| IIIA/B | 5 (18%) | 10 (37%) | 15 (27%) |
| IV | 2 (8%) | 2 (7%) | 4 (7%) |

number (proportion in %); median (minimum-maximum); mean ± standard deviation; Abbreviations: ASA= Classification of American Society of Anesthesiologists; BMI= body mass index; RIPC= remote ischemic preconditioning; UICC= Union for international cancer control

**Table 1: Baseline characteristics of the study cohort**

|  |  |  |  |
| --- | --- | --- | --- |
|  | RIPC (n= 28) | Sham (n= 27) | Overall Cohort(n= 55) |
| **Propofol application** | 26 (93%) | 23 (85%) | 49 (89%) |
| only for induction of anesthesia | 21 (81%) | 18 (78%) | 39 (80%) |
| only for anesthesia maintenance | 0 (0%) | 1 (4%) | 1 (2%) |
| for induction and maintenance | 5 (19%) | 4 (17%) | 9 (18%) |
| **Surgical approach** |  |  |  |
| abdominal approach |  |  |  |
| robotic | 7 (25%) | 11 (41%) | 18 (33%) |
| laparoscopic | 20 (71%) | 16 (59%) | 36 (65%) |
| open | 1 (4%) | 0 (0%) | 1 (2%) |
| thoracic approach |  |  |  |
| robotic | 22 (79%) | 22 (81%) | 44 (80%) |
| thoracoscopic | 5 (18%) | 3 (11%) | 8 (15%) |
| open | 1 (4%) | 1 (4%) | 2 (4%) |
| none | 0 (0%) | 1 (4%) | 1 (2%) |
| **Duration of surgery** [minutes] | 380 (254-610) | 372 (65-548) | 379 (65-610) |
| **Intraoperative blood loss** [ml] | 300 (50-1500) | 300 (100-1500) | 300 (50-1500) |
| **Anastomosis\*** |  |  |  |
| location |  |  |  |
| cervical | 2 (7%) | 0 (0%) | 2 (4%) |
| thoracic | 26 (93%) | 27 (100%) | 52 (95%) |
| technique |  |  |  |
| end-to-end | 1 (4%) | 3 (12%) | 4 (7%) |
| side-to-side | 5 (18%) | 8 (31%) | 13 (24%) |
| end-to-side | 22 (79%) | 15 (58%) | 37 (69%) |
| Suturing technique |  |  |  |
| Hand sewn | 1 (4%) | 0 (0%) | 1 (2%) |
| Linear stapling | 7 (25%) | 8 (31%) | 15 (27%) |
| Circular stapling | 20 (74%) | 18 (69%) | 38 (70%) |

number (proportion in %); median (minimum-maximum); mean ± standard deviation; Abbreviations: RIPC= remote ischemic preconditioning; \*1 patient did not receive an anastomosis

**Table 2: Surgical procedures and intraoperative outcomes**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | RIPC (n= 28) | Sham (n= 27) | Overall Cohort(n= 55) | p |
| Primary outcome |  |  |  |  |
| Anastomotic leakage | 9 (32%) | 9 (35%) | 18 (33%) | 0.847 |
| Severity of anastomotic leakage (ECCG) |  |  |  | 1.000 |
| Grade 2 | 7 (78%) | 7 (78%) | 14 (78%) |  |
| Grade 3 | 2 (22%) | 2 (22%) | 4 (22%) |  |
| Time interval until AL diagnosis [days] | 9 (4-23) | 4 (2-10) | 6.5 (2-23) | **0.013** |
| Reintervention |  |  |  |  |
| Reintervention required | 18 (67%) | 18 (67%) | 36 (65%) | 0.853 |
| Number of reinterventions per patient | 3 (1-20) | 5.5 (1-21) | 4 (1-21) | 0.643 |
| Type of reintervention |  |  |  |  |
| Percutaneous drainage | 8 (29%) | 9 (33%) | 17 (31%) |  |
| Endoscopic vacuum therapy | 9 (32%) | 11 (41%) | 20 (36%) |  |
|  Duration of endoscopic vacuum therapy [days] | 13.5 (4-57) | 11 (4-66) | 13 (4-66) | 0.970 |
|  Number of endoscopic sponge changes | 3 (2-10) | 4 (2-17) | 3 (2-17) | 0.536 |
| Other | 9 (32%) | 10 (37%) | 19 (35%) |  |
| Re-operation | 4 (14%) | 5 (19%) | 9 (16%) | 0.729 |
| AL Grade 3 | 2 (50%) | 2 (40%) | 4 (44%) |  |
| Colon ischemia | 0 | 1 (20%) | 1 (11%) |  |
| Duodenal ulcer perforation | 0 | 1 (20%) | 1 (11%) |  |
| Enterothorax | 1 (25%) | 0 | 1 (11%) |  |
| Pleural empyema | 1 (25%) | 1 (20%) | 2 (22%) |  |
| Postoperative hospital stay  |  |  |  |  |
| Length of postoperative hospital stay [days] | 13.5 (7-84) | 12 (7-84) | 13 (7-84) | 0.303 |
| Intensive care required | 5 (18%) | 4 (15%) | 9 (16%) | 1.000 |
| Length of intensive care [days] | 1 (1-13) | 39 (11-44) | 11 (1-44) | **0.021** |
| Readmission | 5 (18%) | 5 (19%) | 10 (18%) | 1.000 |
| Postoperative 90-day morbidity (Clavien-Dindo) |  |  |  | 0.123 |
| No complications | 5 (18%) | 1 (4%) | 6 (11%) |  |
| Grade I | 1 (4%) | 3 (11%) | 4 (7%) |  |
| Grade II | 2 (7%) | 3 (11%) | 5 (9%) |  |
| Grade IIIa | 15 (54%) | 13 (48%) | 28 (51%) |
| Grade IIIb | 5 (18%) | 2 (7%) | 7 (13%) |  |
| Grade IVb | 0 (0%) | 2 (7%) | 2 (4%) |  |
| Grade V | 0 (0%) | 3 (11%) | 3 (5%) |  |
| Complications (ECCG) |  |  |  |  |
| Conduit necrosis | 0 (0%) | 1 (4%) | 1 (2%) | 0.491 |
| Chyle leak | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Recurrent nerve palsy | 1 (4%) | 0 (0%) | 1 (2%) | 1.000 |
| HMGB1 [ng/ml] |  |  |  |  |
| t0 | 67 (24-178) | 80 (19-318) | 70 (19-318) | 0.457 |
| t1 | 66 (27-129) | 56 (18-268) | 61 (18-268) | 0.628 |
| t2 | 47 (21-161) | 57 (18-218) | 49 (18-218) | 0.522 |
| VEGF [pg/ml] |  |  |  |  |
| t0 | 310 (72-879) | 271 (64-1198) | 294 (64-1198) | 0.849 |
| t1 | 330 (64-1025) | 311 (64-1061) | 379 (64-1061) | 0.628 |
| t2 | 373 (105-1092) | 358 (102-1340) | 468 (102-1340) | 0.665 |

number (proportion in %); median (minimum-maximum); mean ± standard deviation; Abbreviations: AL= anastomotic leakage; ECCG: Esophagus Complications Consensus Group; HMGB1= High-Mobility Group Box 1; RIPC= remote ischemic preconditioning; VEGF= vascular endothelial growth factor

**Table 3: Primary and secondary outcomes**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Anastomotic leakage (n=17) | No anastomotic leakage (n= 36) | p |
| Patient-related factors |  |  |  |
| Age | 61.8 (±6.18) | 63.7 (±127) | 0.407 |
| Sex |  |  | 1.000 |
| Female | 2 (12) | 6 (17%) |  |
| Male | 15 (88%) | 30 (83%) |  |
| BMI | 28.0 (±3.55) | 25.9 (±4.76) | 0.108 |
| ASA score |  |  | 0.713 |
| I | 1 (6%) | 1 (3%) |  |
| II | 12 (71%) | 22 (61%) |  |
| III | 4 (24%) | 12 (33%) |  |
| IV | 0 (0%) | 1 (3%) |  |
| Preoperative Serum Albumin [g/L] | 38.0 (31-43) | 38.7 (25-44) | 0.440 |
| Diabetes mellitus |  |  | 0.205 |
| Yes, insulin dependent | 0 (0%) | 3 (8%) |  |
| Yes, not insulin dependent | 3 (18%) | 2 (6%) |  |
| No | 14 (82%) | 31 (86%) |  |
| Arterial hypertension |  |  | 0.766 |
| Yes | 9 (53%) | 22 (61%) |  |
| No | 8 (47%) | 24 (39%) |  |
| Nicotine abuse |  |  | 0.249 |
| Yes | 12 (71%) | 19 (53%) |  |
| No | 5 (29%) | 17 (47%) |  |
| Pack Years  | 40 (15-80) | 30 (2-120) | 0.369 |
| Alcohol abuse |  |  | 1.000 |
| Yes | 2 (12%) | 5 (14%) |  |
| No | 15 (88%) | 31 (86%) |  |
| Tumor Location |  |  | 1.000 |
| cervical | 0 (0%) | 1 (3%) |  |
| mid thoracic | 3 (18%) | 6 (17%) |  |
| lower thoracic | 5 (29%) | 11 (30%) |  |
| esophagogastric junction | 9 (53%) | 18 (50%) |  |
| Neoadjuvant chemoradiation |  |  | 0.917 |
| Chemotherapy | 11 (65%) | 21 (58%) |  |
| Chemoradiation | 3 (18%) | 9 (25%) |  |
| No | 3 (18%) | 6 (17%) |  |
| Histologic cell type |  |  | 0.293 |
| squamous cell carcinoma | 0 (0%) | 4 (11%) |  |
| adenocarcinoma | 17 (100%) | 32 (89%) |  |
| pT category |  |  | 0.047 |
| T0 | 5 (29%) | 13 (36%) |  |
| T1a,b | 6 (35%) | 5 (14%) |  |
| T2 | 0 (0%) | 9 (25%) |  |
| T3 | 6 (35%) | 9 (25%) |  |
| pL category |  |  | 0.203 |
| L0 | 10 (59%) | 29 (81%) |  |
| L1 | 6 (35%) | 6 (17%) |  |
| LX | 1 (6%) | 1 (3%) |  |
| pPn category |  |  | **0.063** |
| Pn0 | 9 (56%) | 30 (83%) |  |
| Pn1 | 6 (38%) | 5 (14%) |  |
| PnX | 1 (6%) | 1 (3%) |  |
| Distand metastasis |  |  | 0.543 |
| M0 | 16 (94%) | 35 (97%) |  |
| M1 | 1 (6%) | 1 (3%) |  |
| UICC stage |  |  | 0.987 |
| 0 | 5 (29%) | 13 (36%) |  |
| IA/B | 4 (24%) | 7 (19%) |  |
| IIA/B | 2 (12%) | 4 (11%) |  |
| IIIA/B | 5 (29%) | 10 (28%) |  |
| IV | 1 (6%) | 2 (6%) |  |

number (proportion in %); median (minimum-maximum); mean ± standard deviation; Abbreviations: ASA= Classification of American Society of Anesthesiologists; BMI= body mass index; UICC= Union for international cancer control

**Table 4: Results of univariate analysis assessing patient-related risk factors for AL**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Anastomotic leakage (n=17) | No anastomotic leakage (n= 36) | p |
| Technical factors |  |  |  |
| Propofol application |  |  | **1.000** |
| Yes | 15 (88%) | 32 (89%) |  |
| No | 2 (12%) | 4 (11%) |  |
| Surgical approach |  |  |  |
| abdominal approach |  |  | 0.147 |
| robotic | 7 (41%) | 10 (28%) |  |
| laparoscopic | 9 (53%) | 26 (72%) |  |
| open | 1 (6%) | 0 (0%) |  |
| thoracic approach |  |  | 1.000 |
| robotic | 14 (82%) | 29 (81%) |  |
| thoracoscopic | 3 (18%) | 5 (14%) |  |
| open | 0 (0%) | 2 (5%) |  |
| Intraoperative blood loss [ml] | 250 (50-1500) | 300 (100-1500) | 0.315 |
| Duration of surgery [minutes] | 381 (254-598) | 381 (315-610) | 0.819 |
| Anastomosis |  |  |  |
| location |  |  | 0.543 |
| cervical | 1 (0%) | 1 (3%) |  |
| thoracic | 16 (94%) | 35 (97%) |  |
| technique |  |  | 0.889 |
| end-to-end | 1 (6%) | 3 (8%) |  |
| side-to-side | 5 (29%) | 8 (22%) |  |
| end-to-side | 11 (65%) | 25 (69%) |  |
| Suturing technique |  |  | 0.232 |
| Hand sewn | 1 (6%) | 0 (0%) |  |
| Linear stapling | 6 (35%) | 9 (25%) |  |
| Circular stapling | 10 (59%) | 27 (75%) |  |
| Lymphadenectomy |  |  | 0.543 |
| 2-field | 16 (94%) | 35 (97%) |  |
| 3-field | 1 (6%) | 1 (3%) |  |
| R-Status |  |  | 0.293 |
| R0 | 17 (100%) | 32 (89%) |  |
| R1 | 0 (0%) | 4 (11%) |  |
| Blood markers |  |  |  |
| VEGF [pg/ml] |  |  |  |
| t0 | 231 (72-1091) | 324 (80-1198) | **0.054** |
| t1 | 255 (64-928) | 397 (77-1061) | **0.067** |
| t2 | 337 (105-1304) | 409 (104-1340) | 0.223 |
| HMGB1 [ng/ml] |  |  |  |
| t0 | 66 (23-121) | 71 (19-318) | 0.568 |
| t1 | 54 (22-114) | 64 (18-268) | 0.189 |
| t2 | 48 (18-157) | 49 (21-218) | 0.371 |

number (proportion in %); median (minimum-maximum); mean ± standard deviation; Abbreviations: BMI= body mass index; VEGF= vascular endothelial growth factor; HMGB1= high-mobility group box 1

**Table 5: Results of univariate analysis assessing surgical characteristics and blood markers as risk factors for AL**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **OR** | **95% CI** | **p** |
| VEGF t1 | 0.997 | 0.994-1.000 | 0.099 |

Variables with p<0.10 in univariate Analysis (Table 4, 5) were assessed for prognostic effects for AL with multivariate logistic regression. Variables VEGF t0, pT, pPn were assessed as not significant effects due to logistic regression backwards elimination.

**Table 6: Results of multivariate logistic regression analysis assessing risk factors for AL**