International Journal of Cardiology 407 (2024) 132027

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Short communication

Decreased clinical performance in TGA-ASO patients after RVOT interventions; a multicenter European collaboration

Leo J. Engele [a,1,2], Víctor González-Fernández [b,1,2], Barbara J.M. Mulder [a,2], Francisco Javier Ruperti-Repilado [c,2], Raquel Ladrón Abia [j,2], Kim van der Vlist [a,2], Francisco Buendía [d,2], Joaquin Rueda [d,2], Harald Gabriel [e,2], Lore Schrutka [e,2], Judith Bouchardy [f,g,2], Markus Schwerzmann [h,2], Mathias Possner [h,2], Matthias Greutmann [i,2], Pastora Gallego [j,2], Magalie Ladouceur [k,2], Monique R.M. Jongbloed [l,2], Daniel Tobler [c,2], Laura Dos [b,3,2], Berto J. Bouma [a,*,2,3]

[a] CAHAL, Center for Congenital Heart Disease Amsterdam-Leiden, location Amsterdam University Medical Center, Amsterdam, the Netherlands
[b] Hospital Universitari Vall d'Hebron, CIBERCV and European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart (ERN GUARD Heart), Barcelona, Spain
[c] University Hospital, University of Basel, Switzerland
[d] Hospital Universitari i Politècnic La Fe and CIBERCV, València, Spain
[e] Medical University of Vienna, Austria
[f] University Hospital Lausanne, Switzerland
[g] University Hospital of Geneva, Switzerland
[h] Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[i] University Heart Center Zurich, Switzerland
[j] Hospital Universitario Virgen del Rocio and European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart (ERN GUARD Heart), Seville, Spain
[k] Hôpital Européen Georges Pompidou, AP-HP, Paris Cité University, Centre de Recherche Cardiovasculaire de Paris, INSERM U970, Paris, France
[l] CAHAL, Center for Congenital Heart Disease Amsterdam-Leiden, location Leiden University Medical Center, Department of Cardiology and Anatomy & Embryology, Leiden, the Netherlands

ARTICLE INFO

Keywords:
Transposition of the great arteries
Arterial switch operation
Right ventricular outflow tract obstruction
Re-intervention
Peak-VO2

ABSTRACT

Background: In patients with transposition of the great arteries and an arterial switch operation (TGA-ASO) right ventricular outflow tract (RVOT) obstruction is a common complication requiring one or more RVOT interventions.
Objectives: We aimed to assess cardiopulmonary exercise capacity and right ventricular function in patients stratified for type of RVOT intervention.
Methods: TGA-ASO patients (≥16 years) were stratified by type of RVOT intervention. The following outcome parameters were included: predicted (%) peak oxygen uptake (peak VO2), tricuspid annular plane systolic excursion (TAPSE), tricuspid Lateral Annular Systolic Velocity (TV S′), right ventricle (RV)-arterial coupling (defined as TAPSE/RV systolic pressure ratio), and N-terminal proBNP (NT-proBNP).
Results: 447 TGA patients with a mean age of 25.0 (interquartile range (IQR) 21–29) years were included. Patients without previous RVOT intervention ($n = 338$, 76%) had a significantly higher predicted peak VO2 (78.0 ± 17.4%) compared to patients with single approach catheter-based RVOT intervention (73.7 ± 12.7%), single approach surgical RVOT intervention (73.8 ± 28.1%), and patients with multiple approach RVOT intervention (66.2 ± 14.0%, $p = 0.021$). RV-arterial coupling was found to be significantly lower in patients with prior catheter-based and/or surgical RVOT intervention compared to patients without any RVOT intervention ($p = 0.029$).

* Corresponding author at: Department of Cardiology, location Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
E-mail address: b.j.bouma@amsterdamumc.nl (B.J. Bouma).
[1] Shared first authorship, these authors contributed equally to this work.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation
[3] Shared last authorship.

https://doi.org/10.1016/j.ijcard.2024.132027
Received 23 July 2023; Received in revised form 13 March 2024; Accepted 4 April 2024
Available online 5 April 2024
0167-5273/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Conclusions: TGA patients after a successful arterial switch repair have a decreased exercise capacity. A considerable amount of TGA patients with either catheter or surgical RVOT intervention perform significantly worse compared to patients without RVOT interventions.

1. Introduction

Patients with D-transposition of the great arteries (TGA) are nowadays surgically treated by the arterial switch operation (ASO) [1]. Although TGA-ASO patients have an excellent late survival [2,3], residual sequelae after ASO are substantial, including right ventricular outflow tract (RVOT) obstruction requiring one or more RVOT interventions in up to 21% at the age of 20 [4]. Data on the long-term impact of RVOT obstruction (RVOTO) and necessary RVOT intervention(s) on clinical performance are scarce. Therefore, we aimed to assess the impact of RVOT interventions on the contemporary cardiopulmonary exercise capacity and right ventricular function of TGA-ASO patients.

2. Methods

2.1. Study population

This multicenter cross-sectional observational study was performed in TGA-ASO patients (≥16 years) from the EPOCH (European Collaboration for Prospective Outcome Research in Congenital Heart disease) [5]. Written informed consent was obtained in all patients and the present study was conducted according to the ethical guidelines of the Declaration of Helsinki. Patients underwent a comprehensive clinical workup including standardized cardiopulmonary exercise test (CPET) and transthoracic echocardiography (TTE). Examinations were performed according to a uniform EPOCH-ASO study protocol. Patients were stratified by type of intervention at the pulmonary valve, main pulmonary artery or pulmonary branches, including; (1) no RVOT intervention; (2) single approach catheter-based intervention(s) consisting of patients with one or more RVOT catheter-based intervention (s); (3) single approach surgical RVOT intervention; (4) multiple approach consisting of patients with a history of both catheter-based and surgical intervention(s) at the RVOT (Fig. 1). Only RVOT interventions performed after the ASO were included in the analysis. In this study we aimed to investigate solely the impact of RVOT obstruction and intervention on exercise performance and ventricular function parameters, to avoid potential confounding effects of other cardiac interventions on the outcome parameters we excluded patients with interventions at the left ventricular outflow tract (LVOT) or device implantation. In addition, patients were stratified between normal and elevated RV systolic pressure (RVSP); elevated RV pressure was defined as RVSP ≥35 mmHg. RVSP was calculated using the maximal tricuspid regurgitation jet velocity and estimated right atrial pressure (Bernoulli equation). The following variables were investigated among the subgroups: predicted (%) peak oxygen uptake (peak VO2) and maximum heart rate during CPET, NT-pro-BNP, tricuspid annular plane systolic excursion (TAPSE), tricuspid Lateral Annular Systolic Velocity (TV S′) and right ventricle (RV)-arterial coupling (defined as TAPSE/RVSP ratio) [6] (Fig. 1).

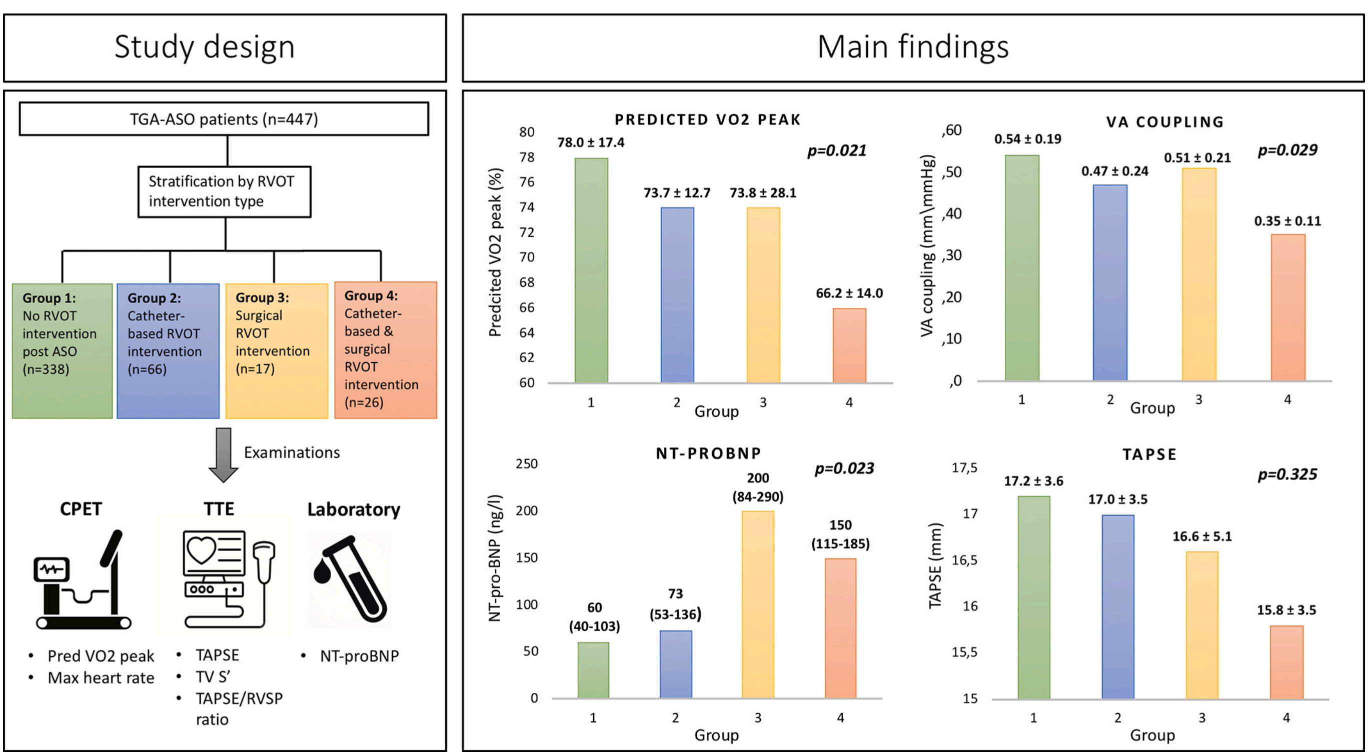

Fig. 1. Study design and main findings.
Fig. 1 shows study design and main findings in TGA-ASO patients, stratified by RVOT intervention technique. Differences between subgroups were determined with one-way ANOVA.
Abbreviations; ASO: arterial switch operation; CPET: cardio pulmonary exercise test; TAPSE: tricuspid annular plane systolic excursion; TGA: transposition of the great arteries; TTE: transthoracic echocardiography; TV S′: tricuspid lateral annular systolic velocity; VA: ventricular-arterial; VO2 peak: peak oxygen.

2.2. Statistical analysis

Continuous normally distributed data are presented as mean (standard deviation (SD)) and non-normally distributed data as median (interquartile range (IQR)). In the main analysis we focused at differences in patient characteristics, exercise performance, ventricular function, and laboratory results among the subgroups stratified for RVOT intervention technique. Differences among these subgroups were investigated by univariate analysis with one-way ANOVA for continues variables with normal distribution and Chi-square for categorical variables. Furthermore, the impact of elevated RVSP on exercise performance and ventricular function among subgroups stratified for RVOT intervention technique was performed by univariate analysis (ANOVA or Chi-square, where appropriate). A p-value <0.05 was considered statistically significant. Statistical analysis was performed using R v.4.2.1 studio (RStudio, Boston, MA).

3. Results

3.1. Baseline characteristics

A total of 475 TGA-ASO patients were identified from the EPOCH consortium. After excluding patients with previous intervention(s) at the LVOT or device implantation ($n = 28$) we included 447 TGA-ASO patients for the analysis. Mean age was 25.0 years (IQR 21–29). A total of 336 (75%) TGA-ASO patients were operated before 2000, we found no significant differences between the RVOT intervention rate, exercise performance and echo parameters between patients operated by the ASO before 2000 and patients operated after 2000. However, patients operated before 2000 had significantly higher NT-proBNP levels ($p = 0.001$) compared to patients operated after 2000 (Supplemental table 1). All patients underwent echocardiographic examination and 275 (62%) patients were examined by CPET. Comparison between patients with and without CPET examination showed a significantly higher RVOT intervention rate in patients who underwent CPET examination (28% vs 20%, $p = 0.001$). However, we did not find any significant differences on patient characteristics or echocardiographic parameters (Supplemental table 2). Heart failure and myocardial infarction were more frequently found in patients with RVOT intervention (Table 1). No differences were found in age, sex or TGA subtype between patients with and without RVOT intervention.

3.2. Subgroups stratified by RVOT intervention technique

Sixty-six (15%) patients underwent single approach catheter-based RVOT intervention(s), 17 (4%) patients had single approach surgical RVOT intervention and 26 (6%) patients underwent a multiple approach including catheter-based and surgical RVOT intervention. In the total cohort, Fifty-two (12%) patients had an increased RVSP (≥35 mmHg).

3.3. Cardiopulmonary exercise capacity

Patients without a RVOT intervention ($n = 338$, 76%) had a significantly higher predicted peak VO2 (78.0 ± 17.4%) compared to those with a RVOT intervention. Moreover, patients with single approach catheter-based RVOT intervention (predicted peak VO2: 73.7 ± 12.7%) or single approach surgical RVOT intervention (predicted peak VO2: 73.8 ± 28.1%) had a better exercise performance than those with both a catheter-based and surgical RVOT intervention (peak VO2: 66.2 ± 14.0%, $p = 0.021$) (Table 1). In patients without any intervention but with elevated RVSP the VO2 peak was lower compared to those with a normal RVSP (71.8 ± 14.3% and 78.8 ± 17%, respectively, $p = 0.001$). Also in patients with multiple approach RVOT procedures a significant lower peak VO2 was found when RVSP was elevated compared to patients with normal RVSP (68.2 ± 17.5%, 61.0 ± 15.7%, respectively, p = 0.001).

Table 1
Demographics and clinical outcome between TGA-ASO patients with no previous RVOT intervention, catheter-based RVOT intervention and/or surgical RVOT intervention.

		Single approach		Multiple approach	
	No RVOT intervention (n = 338)	Catheter-based (n = 66)	Surgical (n = 17)	Catheter-based & surgical (n = 26)	p-value
Patient demographics					
age, yr	25 ± 5.6	25 ± 5.6	27 ± 5.8	25 ± 4.7	0.150
female, n (%)	111 (33)	21 (32)	6 (35)	8 (31)	0.998
TGA subtype, n (%)					
simple	247 (73)	47 (71)	13 (76)	17 (65)	
complex	91 (27)	19 (29)	4 (24)	9 (35)	0.824
Era of ASO (⟨2000), n (%)	242 (72)	52 (78)	16 (94)	17 (65)	0.132
Comorbidities					
myocardial infarction, n (%)	10 (3)	3 (5)	3 (18)	2 (8)	**0.021**
valvular dysfunction, n (%)	61 (18)	9 (14)	3 (18)	4 (15)	0.873
heart failure, n (%)	14 (4)	4 (6)	3 (18)	0 (0)	**0.043**
SVT, n (%)	17 (5)	3 (5)	1 (6)	1 (4)	0.964
CPET					
pred VO2 peak, %	78.0 ± 17.4	73.7 ± 12.7	73.8 ± 28.1	66.2 ± 14.0	**0.021**
max heart rate, b/m	175 ± 16	179 ± 13	176 ± 11	165 ± 25	0.074
Echocardiography					
LVEF (%)	58 ± 7	60 ± 6	55 ± 10	60 ± 9	0.091
LVESD, mm	33 ± 6	32 ± 5	33 ± 12	34 ± 9	0.325
LVEDD, mm	49 ± 7	47 ± 5.5	51 ± 10	47 ± 7	0.055
RVSP, mmHg	34 ± 10	39 ± 15	34 ± 9	51 ± 13	0.532
TAPSE, mm	17.2 ± 3.6	17.0 ± 3.5	16.6 ± 5.1	15.8 ± 3.5	0.325
TV S′, cm/s	9.1 ± 2.4	8.6 ± 2.1	8.5 ± 2.9	8.2 ± 2.1	0.125
VA coupling, mm/mmHg	0.54 ± 0.19	0.47 ± 0.24	0.51 ± 0.21	0.35 ± 0.11	**0.029**
Laboratory					
NT-proBNP, ng/L	60 (40–103)	73 (53–136)	200 (84–290)	150 (115–185)	**0.023**

Demographics and clinical outcome between TGA-ASO patients with no previous RVOT intervention, catheter-based RVOT intervention and/or surgical RVOT intervention. P-values based on one-way ANOVA or chi-square. Abbreviations; ASO: arterial switch operation; CPET: cardio pulmonary exercise test; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; NT-proBNP: N-terminal proBNP; RVSP: right ventricle systolic pressure; SVT: supraventricular tachycardia; TAPSE: tricuspid annular plane systolic excursion; TGA: transposition of the great arteries; TV S′: tricuspid lateral annular systolic velocity; VA: ventricular-arterial; VO2 peak: peak oxygen."

3.4. Echocardiography and laboratory parameters

RV-arterial coupling was found to be significantly lower in patients with prior catheter-based and/or surgical RVOT (re)intervention compared to those without any RVOT (re)intervention (p = 0.029). (Table 1). Systolic right ventricular function, measured by TAPSE, showed a trend to be preserved in patients without RVOT (re)interventions (17.2 ± 3.6 mm) compared to those with a prior catheter based (17.0 ± 3.5 mm), surgical (16.6 ± 5.1 mm) or patients with combined procedures (15.8 ± 3.5 mm), although not statically significant (p = 0.325) (Table 1). In our study, NT-proBNP levels were significantly increased in patients with single approach catheter-based RVOT intervention (median 73 ng/l, IQR 40–103), single approach surgical RVOT intervention (median 200 ng/l, IQR 84–290) and in patients with multiple approach RVOT intervention (median 150 ng/l, IQR 115–185, p = 0.023).

4. Discussion

This large international TGA-ASO EPOCH cohort shows that TGA-ASO patients have an over 20% lower exercise capacity compared to their healthy pears. Furthermore, patients with either a catheter and/or surgical RVOT (re)intervention have a significantly worse clinical performance.

The arterial switch is nowadays associated with low mortality [7] and therefore attention is directed towards long-term morbidity, associated with RVOTO. RVOTO is the most commonly reported complication after ASO [8] and mainly caused by stretch of the pulmonary artery branches caused by the LeCompte maneuver and compression of the pulmonary artery by neoaortic root dilatation. The association between RVOT obstruction with altered pulmonary blood flow distribution and reduced exercise performance has been reported previously [9,10], although clinical performance in patients after restoration of RVOTO by catheter and/or surgical intervention is largely unknown. The findings of our study indicate that even after restoration of blood flow in patients with successful catheter and/or surgical intervention clinical performance is still impaired. Of the echocardiographic RV systolic function parameters, RV-arterial coupling emerged as the most sensitive parameter for assessing hemodynamic RV performance. Utility of the TAPSE/RVSP ratio has recently been reported as a valid surrogate of invasively RVend-systolic/arterial elastance ratio in patients with pulmonary arterial hypertension [6]. In this study patients with both catheter and surgical RVOT interventions showed the lowest value of RV-arterial coupling. In these patients, TAPSE/RVSP ratio probably serves as an early functional marker for RV dysfunction.

4.1. Limitations

This cross-sectional study is subject to the limitations of the observational study design. Echocardiographic and CPET examination were performed according to the study protocol, however we were not able to perform core-laboratory analysis of this data. The number of patients who underwent CPET was significantly higher in patients with RVOT intervention, therefore our study may be susceptible to selection bias. Furthermore, heart failure and myocardial infarction were more frequently found in patients with RVOT intervention, the presence of these comorbidities could also negatively impact exersice performance. Finally, the significantly higher NT-proBNP values found in patients operated before 2000 could suggest that the era of operation influences outcome in TGA-ASO patients. Although, in this study we did not find statistically significant differences in ventricular function and exercise performance between both era's.

5. Conclusion

The current study shows that TGA patients after a successful arterial switch repair have a decreased exercise capacity. A considerable amount of TGA patients with either single approach catheter-based or single approach surgical RVOT intervention perform significantly worse, while those with multiple approach RVOT procedures have the poorest exercise performance. Optimal initial arterial switch repair is of upmost importance for late clinical outcome.

Author statement

All authors have read and approved the manuscript and agree with its submission to the International Journal of Cardiology. The manuscript is not being considered for publication elsewhere and has not been published previously. We hope that you will consider this manuscript for publication in the International Journal of Cardiology and look forward hearing from you at your earliest convenience.

CRediT authorship contribution statement

Leo J. Engele: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Víctor González-Fernández:** Conceptualization, Data curation, Writing – review & editing. **Barbara J.M. Mulder:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. **Francisco Javier Ruperti-Repilado:** Data curation, Writing – review & editing. **Raquel Ladrón Abia:** Writing – review & editing. **Kim van der Vlist:** Writing – review & editing. **Francisco Buendía:** Writing – review & editing. **Joaquin Rueda:** Writing – review & editing. **Harald Gabriel:** Writing – review & editing. **Lore Schrutka:** Writing – review & editing. **Judith Bouchardy:** Writing – review & editing. **Markus Schwerzmann:** Writing – review & editing. **Mathias Possner:** Writing – review & editing. **Matthias Greutmann:** Writing – review & editing. **Pastora Gallego:** Writing – review & editing. **Magalie Ladouceur:** Writing – review & editing. **Monique R.M. Jongbloed:** Supervision, Writing – review & editing. **Daniel Tobler:** Writing – review & editing. **Laura Dos:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Berto J. Bouma:** Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132027.

References

[1] A.D. Jatene, V.F. Fontes, P.P. Paulista, et al., Anatomic correction of transposition of the great vessels, J. Thorac. Cardiovasc. Surg. 72 (1976) 364–370.

[2] T.A. Fricke, I.E. Konstantinov, Arterial switch operation: operative approach and outcomes, Ann. Thorac. Surg. 107 (2019) 302–310.

[3] L.J. Engele, R.L. van der Palen, R.S. Joosen, et al., Clinical Course of TGA After Arterial Switch Operation in the Current Era, JACC: Advances 3 (2) 100772.

[4] B. Santens, A. Van De Bruaene, P. De Meester, et al., Outcome of arterial switch operation for transposition of the great arteries. A 35-year follow-up study, Int. J. Cardiol. 316 (2020) 94–100.

[5] F.J. Ruperti-Repilado, M. Ladouceur, P. Gallego, et al., Comprehensive long-term follow up of adults with arterial switch operation-European collaboration for prospective outcome research in congenital heart disease (EPOCH-ASO)-study design and protocols, Congenit. Heart Dis. 15 (2020) 309–338.

[6] K. Tello, J. Wan, A. Dalmer, et al., Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension, Circ. Cardiovasc. Imaging 12 (2019) e009047.

[7] C.D. Fraser Jr., M.A. Chacon-Portillo, A. Well, et al., Twenty-three-year experience with the arterial switch operation: expectations and long-term outcomes, Semin. Thorac. Cardiovasc. Surg. 32 (2020) 292–299.

[8] R.L.F. van der Palen, N.A. Blom, I.M. Kuipers, et al., Long-term outcome after the arterial switch operation: 43 years of experience, Eur. J. Cardiothorac. Surg. 59 (2021) 968–977.
[9] A. Giardini, S. Khambadkone, N. Rizzo, et al., Determinants of exercise capacity after arterial switch operation for transposition of the great arteries, Am. J. Cardiol. 104 (2009) 1007–1012.
[10] V.J. Baggen, M.M. Driessen, F.J. Meijboom, et al., Main pulmonary artery area limits exercise capacity in patients long-term after arterial switch operation, J. Thorac. Cardiovasc. Surg. 150 (2015) 918–925.