# Correlation between clinical outcomes and patients' satisfaction using tarsoconjunctival - Hughes flap for the reconstruction of eyelid defects

Nina Jovanović<sup>1,2</sup>, Patricia Reisz-Majić<sup>3,4</sup>, Sunita Mehic-Fazlić<sup>5</sup>, Selma Terzić<sup>6</sup>, Jasmina Alajbegović-Halimić<sup>7</sup>, Admira Dizdarević<sup>1</sup>

<sup>1</sup>Ophthalmology Department, Cantonal Hospital Zenica, <sup>2</sup>School of Medicine, University of Zenica; Zenica, Bosnia and Herzegovina, <sup>3</sup> Eye Clinic, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia, <sup>4</sup>University Hospital Centre Osijek, Croatia, <sup>6</sup>Otorhinolaryngology Department, Canton Hospital Zenica, Zenica, <sup>6</sup>Sarajevo Canton Emergency Medical Service, <sup>7</sup>Private Ophthalmology Practice, "Dr. Halimić"; Sarajevo, Bosnia and Herzegovina

#### ABSTRACT

Aim To examine and quantify patients' satisfaction and correlate with the objective clinical presentation after the treatment and to present a comprehensive literature review on tarsoconjunctival/ Hughes flap technique.

**Methods** A review of more than 159 peer-review articles and a combined retrospective-prospective two-centres case series of 17 patients who underwent a two-stage modified Hughes flap procedure (2019-2021) to repair a lower eyelid defect caused by epithelial cancer was conducted. All patients were followed up for a minimum of six months. Patient macroscopic evaluation of redness, lid position, retraction, trichiasis, conjunctival overgrowth, tissue inflammation/infection and hypertrophic scarring were obtained, and findings were graded on a scale of 1 to 5 or binary YES/NO scale. Patients' satisfaction using a Likert-type scale and correlation with the clinical presentation were analysed.

**Results** Pearson correlation coefficient between patients' satisfaction and clinical presentation was 0.534. Out of 510 (the highest summed score for patients' satisfaction), the total score was 479 (93.9%); out of 187 (the highest summed score for clinical presentation), the total score was 162 (86.6%). Although both scores were high, a lower correlation coefficient and the higher satisfaction score can be explained by more realistic expectations in oncological patients compared to cosmetic ones.

**Conclusion** Hughes flaps provide multiple benefits in the reconstruction of selected patients with large defects, especially when poor wound healing is expected, or when local advancement flaps do not provide tension-free reconstruction. The rate of complications is low and manageable, whereas additional therapy is usually observational or symptomatic.

Key words: epithelial malignant skin tumour, Likert score, periocular region

#### **Corresponding author:**

Nina Jovanović Ophthalmology Department, Canton Hospital Zenica, Zenica Phone: +387 32 447 286; Fax: +387 32 226 576; Email: nina-jovanovic@uiowa.edu ORID ID: https://orcid.org/0000-0002-8003-0837

Original submission: 26 August 2022; Revised submission: 12 September 2022; Accepted: 28 October 2022 doi: 10.17392/1531-22

## INTRODUCTION

Tarsoconjunctival (TC) or Hughes flap is used for the reconstruction of large lower eyelid defects which involve 50-70% of the eyelid. Other indications include cutaneous malignancy (1), lid retraction (2), trauma or orbital implant exposure (3), globe rupture (4), congenital and acquired defects. (5,6). The Hughes procedure was initially described by Dr Wendel Hughes in 1937 (7). He followed Gradengio's principle replacing "like with like" (8). The vascularized conjunctival flap overlaid the cornea after the lower eyelid repair with upper and lower lids closed, divided in a second-step procedure. Over the next decades, the procedure evolved and modifications were introduced by Hughes and others (9,10) in an attempt to minimize the number of complications by sparing the marginal upper lid tarsus and removing the levator muscle complex from the tarsoconjunctival flap and changing the location of the lid-splitting incision to minimize the adverse effect of this method (11).

There is controversial evidence in the literature advocating for or against Hughes flap reconstruction technique. One of the recurring controversies in the literature as well as in practice is the choice between Hughes flap combined with a free skin graft (12,13), free tarsoconjunctival (TC) graft combined with myocutaneous flap (14) or free tarsal graft with free skin graft (15) for eyelid defects reconstruction.

The aim of this study was to present objective clinical outcomes (complications and benefits), and correlate individual subjective satisfaction during and post-surgery and estimate overall success.

#### PATIENTS AND METHODS

#### Patients and study design

The retrospective-prospective two-centres study included all patients who underwent a lower eyelid defect repair using the Hughes flap due to primary or recurrent epithelial malignant skin tumour from January 2019 until January 2021 in the Eye Clinic University Clinical Centre Osijek, Croatia, and the Ophthalmology Department of the Cantonal Hospital Zenica, Bosnia and Herzegovina. Exclusion criteria included extensive defects that could not be repaired using a TC flap, malignant tumours other than epithelial origin with metastasis, tumours extending in the orbit, and defective posterior lamella of the upper eyelid. All patients were followed up for a minimum of six months.

Photos were prospectively collected for the analysis before and after surgery (one, three and six months) for an independent reviewer evaluation. A patient macroscopic evaluation of lid colour and lid position were either graded on a numerical scale of 1 to 3 by both surgeons independently, attributing lowest number to the least favourable result, i.e. 1 equals poor result (decolorization, dark pigmentation or other deviations from surrounding skin colour), 2 equals good results (minimally visible changes to surrounding skin colour) and 3 equals excellent results (no visible change compared to surrounding skin); the presence of lid entropion, retraction, trichiasis, conjunctival overgrowth and hypertrophic scarring was noted using YES/NO categorical values by surgeons independently, and assigned value 0 for YES and 1 for NO for further analysis. For each patient, the total score of clinical presentation success was calculated where 11 was the maximum value.

The next was a patient satisfaction questionnaire after a 6-month follow-up via telephone interview or in-person visit using a common rating scale, Likert-type scale (16), generally used for survey research. Patient satisfaction with the surgery end-results via telephone interview using a grading scale of 5 to 1 that best describes patients' satisfaction with the surgery was used. The following grading system of statements was obtained: complete agreement, agreement, indecision/neutrality, disagreement, and complete disagreement, graded from 5 to 1, respectively (Table 2).

Additionally, a literature search was performed twice. First time using "tarsoconjunctival flap AND lower eyelid" and second time using "tarsoconjunctival flap AND/OR Hughes flap" with Boolean Operator "AND/OR". The first search generated 159 peer-reviewed and 292 full text and the second 37 peer-reviewed and 71 full text articles. Only peer-reviewed studies that included lower eyelid defects repaired using classical or modified tarsoconjunctival flap were reviewed and discussed.

The Ethical Committees of the Eye Clinic University Clinical Centre Osijek and the Cantonal Hospital Zenica approved the study (R2-3775/2022 and 00-03-35-38-12/22, respectively). An informed consent was obtained as a part of the informed consent for the surgical procedure.

#### Methods

All surgical procedures were done by two oculoplastic surgeons (the first and the second author of the study).

Phase one of surgical technique. The initial surgical excision of the lower lid margin was performed, and the defect was measured by approximating the minimal amount of tissue needed. The ipsilateral upper lid was everted by using a lid retractor (V. Mueller<sup>™</sup>&Co, Becton, Dickinson and Company, U.S.) and the measurement was performed, marking the incision site, and separating tarsus from the overlying muscles preferably by blunt dissection. The tarsoconjunctival flap was then mobilized, transposed and secured to the lower eyelid blepharotomy incision site. Any bleeding of the upper defect was meticulously managed with cautery as this can lead to bleeding or hematoma. The inferior cut edge of the flap and the conjunctiva were sutured with a running 7-0 vicryl suture (17).

When using a full-thickness skin graft for the reconstruction of the anterior lamella, 6-0 or 7-0 absorbing sutures were commonly used, while if a myocutaneous flap was used to replace the anterior lamella, a running 7-0 vicryl suture to fixate the upper edge of the anterior lamellar flap to the upper edge of the Hughes flap was used (17). **Phase two of the surgical technique.** Division

Table 1. Post-surgical clinical characteristics of 17 patients

of the conjunctival pedicle, as the second stage, is done once the graft developed a blood supply (18-20). The procedure was performed in the ambulatory settings ensuring asepsis and analgesia, where the conjunctival flap was cut along the upper edge of the lower eyelid taking care to excise all the excess conjunctiva.

#### Statistical analysis

All variables were categorical and ordinal. For macroscopic evaluation descriptive statistics were performed. Findings were described using ordinal scale: poor, good, excellent; graded on a scale of 1 to 3 for score calculation; or assigned binary value YES vs. NO.

For patients' satisfaction analysis (Likert-type scale) a descriptive statistical analysis and median values were obtained, and the Pearson correlation coefficient was calculated.

#### RESULTS

The study generated results from 17 patients. The mean age was 72.41 (median: 77, range 58-88).

All 17 patients had no entropion, two had lower lid retraction, none had trichiasis and three had conjunctival overgrowth and hypertrophic scarring. Out of 17 patients, 10 had excellent lid position and seven had good; while seven had excellent and ten had good lid colour (Table 1).

Four patients had the score 11, six had the score 10, four had the score 9, one had 8, and two had 7. The sum of scores for all patients was 162, which was 86.6% of the total ideal score of 187.

Patient ordinal number	Age (years)	Lid position*	Lid colour* (poor/good/excellent)	<b>Entropion</b> <sup>†</sup>	Lid retraction <sup>†</sup>	Trichiasis	Conjunctival overgrowth <sup>†</sup>	Hypertrophic scarring <sup>†</sup>
1	58	Excellent	Good	NO	NO	NO	NO	NO
2	82	Excellent	Good	NO	NO	NO	YES	NO
3	61	Excellent	Excellent	NO	NO	NO	NO	NO
4	80	Excellent	Excellent	NO	NO	NO	NO	NO
5	47	Excellent	Good	NO	NO	NO	NO	YES
6	84	Good	Good	NO	YES	NO	NO	YES
7	85	Good	Good	NO	NO	NO	NO	NO
8	49	Good	Excellent	NO	NO	NO	NO	NO
9	85	Good	Good	NO	YES	NO	NO	NO
10	74	Good	Good	NO	NO	NO	NO	NO
11	77	Good	Good	NO	NO	NO	YES	YES
12	88	Good	Excellent	NO	NO	NO	NO	NO
13	80	Excellent	Good	NO	NO	NO	NO	NO
14	72	Excellent	Good	NO	NO	NO	NO	NO
15	60	Excellent	Excellent	NO	NO	NO	NO	NO
16	85	Excellent	Excellent	NO	NO	NO	YES	NO
17	64	Excellent	Excellent	NO	NO	NO	NO	NO

\*(poor/good/excellent); \*YES/NO;

	Sa	tisfaction wit	h		Not having	The most difficult	Total score
Patient ordinal number	Functional result of the operation (opening/closing the eyes)		Aesthetic result of the operation	by symptoms of	inflammation/redness of the operated eye compared to the non-operated	thing for you was between two acts of surgery due to a closed eye	
1	5	5	5	5	5	5	30
2	4	4	3	5	4	4	24
3	5	4	4	5	5	5	28
4	5	5	5	5	5	5	30
5	5	5	4	5	4	4	27
6	5	4	4	4	5	4	26
7	5	5	5	4	5	5	29
8	5	5	5	4	5	5	29
9	5	5	5	3	4	5	27
10	5	5	4	5	4	5	28
11	5	4	4	5	5	5	28
12	5	5	5	4	4	5	28
13	5	5	5	4	4	5	28
14	5	5	5	4	5	5	29
15	5	5	5	4	4	5	28
16	5	5	5	5	5	5	30
17	5	5	5	5	5	5	30
Total score	84/85	81/85	78/85	76/85	78/85	82/85	479

Table 2. Likert score of the individual satisfaction of the post-surgical results

For patients' satisfaction with the end results the sum of scores for patients ranged between 24 and 30, where the former was the lowest and the latter the highest. Out of 17 patients, three had the score 30. The median score was 28. The sum of scores for all patients was 479, which was 93.9% of the total ideal score of 510 (Table 2).

The Pearson correlation coefficient between patients' satisfaction and the clinical results was 0.534 (53.4%).

## DISCUSSION

Viability, vascularization and thus the separation time of the Hughes flap pedicle has been questioned in the literature with controversial results (20-23). Research showed that the flap pedicle does not seem to affect the perfusion of the flap, but the rich vascularization of the eyelid and tear film (21). In that matter, the free skin graft revascularizes within 3 to 8 weeks, despite the previous study results of avascular flap (22). However, several studies indicated that flap vascularization is established between 3 and 4 weeks after without complications (23-25). This shows a gradual decrease in time of pedicle separation and greater comfort for patients using this method. Converging with this, Leibovitch concluded that the separation may be done after 7 days without compromising flap viability (26). Our study results showed good results in terms of flap survival after 3 weeks of lid closure. According to the literature, most surgeons perform the procedure after 3-4 weeks (27). Benefits of early separation include faster recovery, easier monitoring and minimized duration of eye occlusion. However, it has been associated with lower eyelid retraction, especially if the period was less than 2 weeks (18), flap necrosis, corneal abrasion, foreign body sensation, mucous discharge and dry eye (19). Our study did not show any adverse effects following the separation.

According to Hawes, Hughes flaps are more likely to result in eyelid margin erythema compared to other techniques (1). In the Ekin and Ugurlu study, cosmetic outcomes of the surgery are usually defined as satisfactory if the reconstructed lid did not exhibit lagophthalmos, contour irregularity, notching, unmatched colour or noticeable scarring (28). In our study three patients had conjunctival overgrowth that could be managed by additional thermocauterisation; however, lid colour was good or excellent in all patients and there was no need for additional treatment, which is in agreement with results in Hawes's study where several postsurgical complications occurred but none requiring revision (1).

Leibovitch et al. (29) described complications related to FTSG such as hematomas, graft infections, partial or complete graft rejection, hypertrophy or contracture of the graft while Marcet, McNab and colleagues (30,31) found inadequate manipulation of the lobe for the posterior lamella, such as excessive clamping, may contribute to graft rejection. In our study two (out of 17) patients had lower lid retraction, none had trichiasis and three had conjunctival overgrowth and hypertrophic scarring. Ten out of 17 patients had good lid colour versus excellent in 7 patients, but without required additional treatment.

Tear film instability with reduced tear breakup time test and epiphora was described by Zaky and al. (32) and explained by the size of the defect. Similarly, Klein-Theyer et al. (33) concluded that despite the favourable aesthetic and functional results there is a statistically significant difference in tear film quality, meibomian gland loss, subjective symptoms of discomfort, lid margin abnormalities affecting the ocular surface health, explained by the shift in Meimbom glands direction (34). Our patients' series did not examine tear film, however, during interviews, one patient reported more severe dry eye symptoms, while 7 out of 17 reported being mildly bothered by dry eye symptoms.

Skin and conjunctival erythema occur due to vertical contraction of the eyelid, ectropion, lagophthalmos and conjunctival outgrowth, and are dependent on the anterior lamella repair. Since the anterior lamella choice is related to the posterior lamella selection, it is not clear if the posterior lamella type induces erythema (1). In the conclusion, Hawes indicated the size of the primary defect as the main factor in choosing between two surgical procedures, recommending Hughes TC flap for major defects (> 75% of the lower eyelid) or difficult healing within 4 weeks between two acts of surgery (1).

Comorbidities and contraindications for Hughes FC flap due to the need to close the eye for several weeks (e.g. acute angle-closure glaucoma, poor vision contralaterally, development of amblyopia) should be carefully and individually discussed (18).

In case of skin graft hypertrophy, triamcinolone or fluorouracil injections can be applied with simultaneous massage with anti-scar gels. At a later stage,  $CO_2$  laser treatment can be performed. Three patients in our study experienced skin hypertrophy after the surgery but all refused additional treatment for scarring minimization. All patients were administered steroid ointment with massage during postoperative recovery.

According to Zaky et al. nearly half of their case series had to use artificial tears to minimize symptoms from tear film instability and break-up time test decrease (32). For the loss of meibomian glands and tear film instability, therapy is symptomatic in the form of eye surface care. In case of an irregular eyelid margin or hyperaemia caused by an overgrown eyelid margin joint, additional excision with or without thermocauterisation can be performed. In case of lagophthalmos, eyelid ectropion or retraction, surgery is required, most often FTSG with or without additional horizontal shortening or suspension of the lateral edge of the lower eyelid, depending on the laxity of the eyelid. Today, this complication is rare and is more common in the shortened period between two acts of surgery. Less often, additional surgery is needed. However, Perry and Allen suggest using other surgical methods like lateral stabilization with a periosteal strip and myocutaneous advancement flap to avoid often seen complication with Hughes flap (35).

The main limitation of our study is the small sample size. However, the TC flap is a well known and frequently used procedure, thus we aimed to show a broad presentation of benefits and downsizes of this procedure and compare it to different techniques. Additionally, we presented literature evidence of avoiding possible complications and managing adverse effects.

In conclusion, Hughes flaps provide multiple benefits in the reconstruction of large defects occupying more than 70% of lower eyelid loss, especially when poor wound healing is expected or when local advancement flaps do not provide tension-free reconstruction but with contraindication for specific patient groups. The rate of complications and side effects is low and manageable, whereas additional therapy is usually observational or symptomatic.

#### FUNDING

No specific funding was received for this study.

# TRANSPARENCY DECLARATION

Competing interests: None to declare.

#### REFERENCES

- Hawes MJ, Grove AS, Jr., Hink EM. Comparison of free tarsoconjunctival grafts and Hughes tarsoconjunctival grafts for lower eyelid reconstruction. Ophthalmic Plast Reconstr Surg 2011; 27:219-23.
- Juniat V, Ryan T, O'Rourke M, Ng S, O'Donnell B, McNab AA, Selva D. Hughes flap in the management of lower lid retraction. Orbit 2021; 23:1-6.
- Chungkwon YOO M-SP, Tae-Soo LEE. Treatment of recalcitrant orbital implant exposure using upper tarsoconjunctival flap. J Korean Ophthalmo Soc 2001; 1787-92.
- Hughes L, Saxby E, Wright M. Tarsoconjunctival 'Hughes' flap for repair of globe perforation: A modified technique in the management of severe scleral necrosis. Eur J Ophthalmol 2021; 32:NP60-NP63.
- Chen Y, Al-Sadah Z, Kikkawa DO, Lee BW. A Modified Hughes Flap for correction of refractory cicatricial lower lid retraction with concomitant ectropion. Ophthalmic Plast Reconstr Surg 2020; 36:503-7.
- Cho RI. Correction of recalcitrant cicatricial lower lid retraction and entropion with transverse tarsotomy and tarsoconjunctival flap. Ophthalmic Plast Reconstr Surg 2019; 35:91-4.
- WL H. A new method for rebuilding a lower lid. Arch Ophthalmol 1937; 17:1008 –17.
- Yano T, Karakawa R, Shibata T, Fuse Y, Suzuki A, Kuramoto Y, Suesada N, Miyashita H, Yoshimatsu H. Ideal esthetic and functional full-thickness lower eyelid "like with like" reconstruction using a combined Hughes flap and swing skin flap technique. J Plast Reconstr Aesthet Surg 2021; 74:3015-21.
- Hughes WL. Total lower lid reconstruction: technical details. Trans Am Ophthalmol Soc 1976; 74:321-9.
- Rohrich RJ, Zbar RI. The evolution of the Hughes tarsoconjunctival flap for the lower eyelid reconstruction. Plast Reconstr Surg 1999; 104:518-22.
- Cies WA, Bartlett RE. Modification of the Mustardé and Hughes methods of reconstructing the lower lid. Ann Ophthalmol 1975; 7:1497-502.
- Hughes WL. Reconstructive surgery of the eyelids. Adv Ophthalmic Plast Reconstr Surg 1986; 5:25-87.
- Hishmi AM, Koch KR, Matthaei M, Bölke E, Cursiefen C, Heindl LM. Modified Hughes procedure for reconstruction of large full-thickness lower eyelid defects following tumor resection. Eur J Med Res 2016; 21:7.
- 14. Pham CM, Heinze KD, Mendes-Rufino-Uehara M, Setabutr P. Single-stage repair of large full thickness lower eyelid defects using free tarsoconjunctival graft and transposition flap: experience and outcomes. Orbit 2022; 41:178-83.
- Bortz JG, Al-Shweiki S. Free Tarsal Graft and Free Skin Graft for Lower Eyelid Reconstruction. Ophthalmic Plast Reconstr Surg. 2020; 36:605-9.
- Dukes K. Likert Scale. In: Armitage P and Colton T, ed. Encyclopedia of Biostatistics. Chichester: Wiley, 2005: 2786–7.
- 17. Eye Rounds.org The University of Iowa. Hughes Flap (tarsal-conjunctival flap). https://webeye.ophth. uiowa.edu/eyeforum/video/plastics/1/Hughes-Flap. htm (26 October 2022).
- Mandour SS, Kakizaki H, Farahat HG, Hegazi KA, El Saadany AKI, Iwaki M. Use of modified Hughes flap versus auricular cartilage graft for replacement of posterior lamella in lower eyelid reconstruction. J Clinic Experiment Ophthalmol 2011; 0:1-4.

- McKelvie J, Ferguson R, Ng SGJ. Eyelid reconstruction using the "Hughes" tarsoconjunctival advancement flap: Long-term outcomes in 122 consecutive cases over a 13-year period. Orbit 2017; 36:228-33.
- Tenland K, Memarzadeh K, Berggren J, Nguyen CD, Dahlstrand U, Hult J, Engelsberg K, Lindstedt S, Sheikh R, Malmsjö M. Perfusion monitoring shows minimal blood flow from the flap pedicle to the tarsoconjunctival flap. Ophthalmic Plast Reconstr Surg 2019; 35:346-9.
- Memarzadeh K, Gustafsson L, Blohmé J, Malmsjö M. Evaluation of the microvascular blood flow, oxygenation, and survival of tarsoconjunctival flaps following the modified Hughes Procedure. Ophthalmic Plast Reconstr Surg 2016; 32:468-72.
- 22. Berggren J, Tenland K, Ansson CD, Dahlstrand U, Sheikh R, Hult J, Engelsberg K, Lindstedt S, Malmsjö M. Revascularization of free skin grafts overlying modified Hughes tarsoconjunctival flaps monitored using laser-based techniques. Ophthalmic Plast Reconstr Surg 2019; 35:378-82.
- Bartley GB, Messenger MM. The dehiscent Hughes flap: outcomes and implications. Trans Am Ophthalmol Soc 2002; 100:61-5.
- Seyhan NZT, Keskin M, Savaci N. Lower eyelid reconstruction with tarsoconjunctival flap in a xeroderma pigmentosum patient. Eur J Plast Surg 2012; 35:185-7.
- 25. Ibrahim A, Chalhoub RS. 5-fu for problematic scarring: a review of the literature. Ann Burns Fire Disasters 2018; 31:133-7.
- Leibovitch I, Selva D. Modified Hughes flap: division at 7 days. Ophthalmology 2004; 111:2164-7.
- Aggarwal S, Shah CT, Kirzhner M. Modified second stage Hughes tarsoconjunctival reconstruction for lower eyelid defects. Orbit 2018; 37:335-40.
- Ekin MA, Ugurlu SK. Impact of the type of anterior lamellar reconstruction on the success of modified Hughes procedure. Arq Bras Oftalmol 2020; 83:11-8.
- Leibovitch I, Huilgol SC, Hsuan JD, Selva D. Incidence of host site complications in periocular full thickness skin grafts. Br J Ophthalmol 2005; 89:219.
- Marcet MM, Lau IHW, Chow SSW. Avoiding the Hughes flap in lower eyelid reconstruction. Curr Opin Ophthalmol 2017; 28:493-8.
- McNab AA, Martin P, Benger R, O'Donnell B, Kourt G. A prospective randomized study comparing division of the pedicle of modified hughes flaps at two or four weeks. Ophthalmic Plast Reconstr Surg 2001; 17:317-9.
- Zaky AG, Elmazar HM, Abd Elaziz MS. Longevity results of modified Hughes procedure in reconstructing large lower eyelid defects. Clin Ophthalmol 2016; 10:1825-8.
- 33. Klein-Theyer A, Horwath-Winter J, Dieter FR, Haller-Schober EM, Riedl R, Boldin I. Evaluation of ocular surface and tear film function following modified Hughes tarsoconjunctival flap procedure. Acta Ophthalmol 2014; 92:286-90.
- Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000; 118:615-21.
- Perry C, Allen R. Repair of 50-75% full-thickness lower eyelid defects: Lateral stabilization as a guiding principle. Indian J Ophthalmol 2016; 64:563-7.